NHS England

Evidence review: Extracorporeal Membrane Oxygenation (ECMO) for Bridge to Lung Transplant

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1. Introduction

Bridge to Lung Transplant

Lung transplantation is routinely performed for selected patients with respiratory failure. On 31 March 2018 there were 353 patients awaiting lung transplant in the UK. However, approximately 25% of patients on the waiting list die before a suitable donor becomes available or are removed from the waiting list due to deteriorating health rendering lung transplantation futile and inappropriate. There are therefore a substantial proportion of patients who would benefit from ventilatory support to bridge them to transplant (BTT). Traditionally, mechanical ventilation (MV) has formed the mainstay of this bridging support but it is not sufficient for all patients and has been associated with severe complications and poor post-transplant outcomes (Todd et al 2017). Hence MV is now a relatively contraindicated as BTT. An alternative to MV is extracorporeal life support with extracorporeal membrane oxygenation (ECMO) or interventional lung assist (iLA).

Extracorporeal life support (ECLS)

ECMO and iLA are techniques for providing respiratory support for those people whose lungs are no longer able to sustain life despite all other therapeutic and supportive interventions. Treatment is provided for critically ill people in a level 3 critical care area. Blood is removed from the patient's circulation and passes through a gas exchanged device before being returned to the circulation. ECMO removes blood from the venous circulation which is then pumped through a gas exchange device and is returned to either the arterial circulation (veno-arterial (VA) ECMO) or the venous circulation (veno-venous (VV) ECMO). VV ECMO provides respiratory support only whereas VA ECMO can provide full cardiorespiratory support. The iLA relies on patients own arterial blood pressure to drive blood flow from an artery through the iLA typically without a mechanical pump, blood is then returned to the venous circulation. The iLA can allow clearance of carbon dioxide but has limited capacity for oxygenation and no capacity for circulatory support.

Complications

ECMO is an invasive procedure and serious complications are common, including thrombosis and haemorrhage, arrhythmias, neurological and metabolic disturbances; acute tubular necrosis may require hemofiltration and dialysis.

The clinical problem

The clinical question is the role of ECMO in transplant wait-list patients whose clinical condition is critical and deteriorating despite maximal respiratory support, and for whom no organ is available to transplant. Such patients are expected to die within 24 hours unless offered further supportive treatment (i.e. ECMO). Hence it is assumed that ECMO improves overall survival against comparable patients not offered ECMO. The clinical question is whether use of ECMO BTT impairs post-transplant survival or quality of life.

2. Summary of results

Eight studies were used in this review: one systematic review and seven cohort studies containing between 12 and 68 patients on ECMO BTT. All the cohort studies included comparison of post-transplant outcomes in an ECMO BTT cohort and a non-bridged cohort of patients.

Survival

All studies reported 1-year survival, two reported 3-year survival and three reported 5-year survival (in all cases 'survival' means survival after transplant). Results suggest that 70-90% of patients who receive ECMO BTT are still alive at 1 year, around 60-80% are alive at 3 years, and around a 65% are alive at 5 years post-transplant. The rate of survival is no worse in critically ill patients requiring ECMO compared with less ill patients who survive to transplant without ECMO bridging support.

Quality of life and functional status

Health-related quality of life (HRQL) was reported by one study. Patients on ECMO BTT achieved similar improvements in HRQL and depressive symptoms as those who did not require ECMO bridging, these improvements were greatest in the first six months post-transplant and then remained stable at 12 months. Functional status was also assessed in only one study and showed that the 1-year post-transplant functional status of patients on ECMO BTT was equivalent to that of non-bridged patients and could be described as excellent.

Complications

General complications were reported in five studies, acute graft rejection in four studies, long-term graft survival in one study and post-operative ventilation in four studies. Acute graft rejection is not clearly worse in ECMO BTT than non-bridged patients and long-term follow up suggests that overall graft survival is equal. The impact of ECMO BTT on post-transplant ventilation requirements is unclear but the higher rates seen in ECMO BTT patients in some studies may be explained by concurrent MV use. More convincingly though, ECMO BTT is associated with higher rates of some serious complications such as bleeding, delirium, myopathy and vascular and thrombotic events, although the exact magnitude of these risks is difficult to determine due to heterogeneity in the post-transplant outcomes and indicators used in different studies. ECMO BTT is associated with a risk of mortality in patients on this treatment, based on five studies around 20% - 30% of patients die on ECMO before transplantation.

Duration pre-transplant ECMO and length of stay

Duration of ECMO was reported by five studies and ranged from a mean of 3.2 to 15 days. There is little certainty about the exact duration to expect as the ranges are wide within studies, but it appears that duration of treatment does not tend to exceed

around 16 days in the majority of patients. There is a general trend towards the reporting of longer hospital and ITU stays in patients receiving ECMO BTT compared to patients not receiving ECMO before transplant but large variability within and between studies makes it difficult to identify the exact magnitude of difference or indeed be clear about whether any differences are statistically significant.

Awake versus sedated ECMO

One study includes additional data that provides a comparison of post-transplant outcomes in awake and sedated ECMO strategies. There is suggestion that an awake ECMO strategy offers a survival advantage over sedated strategies which use concurrent MV. However, the distinction of awake and sedated care is not relevant to the non-bridged patients so this is a comparison that is made between patients in the ECMO BTT intervention group only.

Cost effectiveness

None of the studies provided any data on cost or cost effectiveness of ECMO BTT.

Interventional Lung Assist (iLA)

None of the studies provided data on iLA.

Limitations

No studies provided data on cost effectiveness of ECMO BTT. As randomised controlled trials are neither practical nor ethical this review included observational studies and a systematic review. Some of the studies had small sample sizes, particularly in the ECMO BTT group, and included patients recruited over long periods of time when ECMO technology and practice may have changed.

3. Methodology

The report aimed to identify and assess the evidence comparing the effectiveness and safety of ECMO as bridge to lung transplant (BTT) compared to best supportive care (no bridging).

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).

A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).

Medline databases using the Pubmed platform were searched for any systematic reviews, clinical trials or observational studies published in the last ten years that

reported post-transplant outcomes for ECMO BTT and iLA (see section 10 for search strategy). Search outputs were reviewed by clinical experts to identify any relevant missing publications.

The outcomes from all papers included were extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).

The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

This evidence review aimed to compare ECMO BTT with supportive care. The literature contained a spread of different groups who had and had not received ECMO BTT and we considered the best comparison to be patients who had received ECMO BTT and patients who had received no bridging support. In studies where other intervention groups were included these are detailed in the description of population characteristics of each study but the outcomes of these additional groups are not reported in the outcome measures and results in section 7 (summary of evidence table).

There was some heterogeneity in the clinical features of the ECMO received by patients in the ECMO BTT groups both within and across the studies, such as the level of sedation and the use of concurrent MV. It was decided to include all studies which fit the inclusion criteria regardless of ECMO procedure used as it is likely that this heterogeneity reflects the differences in clinical practice of ECMO according to patients' needs, and the majority of studies do not report outcomes according to different ECMO procedures. In studies where groups undergoing different ECMO procedures are clearly distinguished, the group receiving the least additional intervention has been selected for inclusion.

No restriction on study post-transplant outcomes was used in the search. All outcomes reported in the included studies are reported in this review. Only papers published in last ten years and including a majority of patients treated in the past 10 years were included. There have been significant advances in ECMO technology, practice and safety over the last decade.

Only papers which reported results for 10 or more patients who underwent ECMO BTT or iLA were included. These procedures are highly technical and including single case reports or small case series might have included poorer outcomes obtained from patients with unusual circumstances (warranting case reports) or centres who have not completed a learning curve. The selection of a threshold of 10 patients is arbitrary but reflects the general distinction between small case series reports and more comprehensively deigned observational studies at larger centres or groups of centres. From a data analysis point of view the exclusion of very small studies also reduces the risk of type 1 and 2 errors (over or underestimating the causal inference).

Full details of the search are available in section 10 (search strategy). In brief, 402 abstracts were screened, and 31 selected for full text review. The reference lists of evidence reviews and eligible studies were screened, and this identified no new eligible studies. Clinical experts were asked to identify further relevant papers, and none were identified. Eight eligible studies were identified which fulfilled the search criteria and the exclusion criteria. These are described in section 11 (evidence

selection). There was discussion with a second reviewer to agree the included papers.

4. Results

Overall results

Eight studies were considered in this review; one systematic review (Chiumello 2015) and seven cohort studies containing between 12 and 68 patients on ECMO BTT (Havanga 2018, Ius 2018, Kolaitis 2018, Lehmann 2015, Schechter 2016, Todd 2017, Toyoda 2013). Of the cohort studies, six were retrospective and one was prospective, six were from a single centre and one used data obtained from an organ sharing database. No papers were found on iLA. Follow-up of ECMO BTT patients and non-bridged patients ranged from 1-year to 5-years. Although each study included a control group of non-bridged patients, the ECMO strategy in the ECMO BTT group varied within and between studies (i.e. whether ECMO BTT alone was given or ECMO+MV). There was also variation in the post-transplant outcomes reported and the measures and indicators used to express these. This heterogeneity makes it difficult to combine the results of studies so instead a descriptive analysis of the results of the post-transplant outcomes has been undertaken for this evidence review.

What is the survival of patients receiving ECMO or iLA as bridge to transplant?

Survival

All studies included post-transplant survival at 1-year as an outcome, two included survival at 3-years and three included it at 5-years.

1-year survival

The proportion of patients surviving to 1-year post-transplant was reported in the two best studies: survival in ECMO BTT and non-bridged patients respectively as 70.4% and 84.2% (Schechter et al 2016), and 79% and 90% (Ius et al 2018).

Similar patterns of survival are reported by four of the remaining studies (Hayanga et al 2018, Todd et al 2017, Lehmann et al 2015 and Toyoda et al 2013) , ranging from 71%-91% in non-bridged patients and 68%-100% in ECMO BTT groups.

Although Todd et al 2017 report 100% survival of ECMO BTT patients at 1-year, they had a small sample size so this may not be a reliable and generalisable estimate of survival in this population.

Kolaitis et al 2018 and Chiumello et al 2015 do not present data for the non-bridged patients, but the remaining studies all found there to be no statistically significant difference between the ECMO BTT and non-bridged patients 1-year survival.

This suggests that 1-year survival in ECMO BTT is equivalent to that of non-bridged patients and is likely to be in the range of 60-80%.

3-year survival

Two studies include data on survival at 3-years post-transplant. One of these is considered one of the best studies in this review (Schechter et al 2016) and reports no significant difference in survival at 3 years for patients on ECMO BTT and those not requiring bridging support (65% vs 67% respectively p = 0.16).

Hayanga et al 2018 also reported no significant difference (P> 0.05) in the rates of survival in patients in ECMO BTT and non-bridged patients (77% vs 73% respectively) .

5-year survival

Three studies report the proportion of patients surviving to 5 years. One of the best studies in this review, Ius et al 2018, report a 5-year post-transplant survival rate of 65% in ECMO BTT (no statistically significant difference compared with non-bridged (71%)). Hayanga et al 2018 also report similar 5-year survival probabilities with no statistically significant difference between tbridged and non-bridged (66% vs 59% respectively), but their ECMO BTT group are all on MV (compared to the majority of the Ius et al 2018 ECMO BTT cohort who are awake and not on MV).

In summary, these results suggest that 70-90% of patients who receive ECMO BTT are still alive at 1-year post-transplant, around 60-80% are alive at 3 years post-transplant, and around a 65% are alive at 5-years post-transplant, and this rate of survival is no different to that of patients not receiving any bridging support.

What is the Quality of Life for patients receiving ECMO as BTT?

Quality of Life and functional status

Health-related quality of life

Health-related quality of life (HRQL) was included in the Kolaitis et al 2018 study. They reported changes in scores on 5 different measures of HRQL from pre-transplant to 6 months post-transplant in patients on ECMO BTT and non-bridged patients.

Before transplantation, HRQL and depressive symptoms were similar among the groups, although non-bridged patients reported better baseline HRQL on two of the surveys (SF12-MCS and EQ5D). After transplantation, HRQL and depressive symptoms generally improved inn both groups. Overall, peak improvement in HRQL and depressive symptoms was seen in the early period, within 6 months post-transplantation, and remained stable through to 12 months post-transplantation. The magnitude of these early improvements at 6 months varied by instrument. The greatest improvement was seen in respiratory-specific HRQL, but there were also substantial improvements in health utility and depressive symptoms, and some improvement in generic mental HRQL.

In summary, patients ill enough to require ECMO BTT achieve similar improvements in HRQL and depressive symptoms as those who are less ill and do not require ECMO bridging support. These improvements are greatest in the 6 months post-transplant and then remain stable to 12 months. There is a low to moderate uncertainly with these conclusions, the study was high quality and used several different measures of HRQL which make the results reliable and valid, but only one study with relatively small sample size included measures of HRQL as an outcome. Additionally, the study only included patients under the age of 65 but used the geriatric depression test to measure changes in depressive symptoms so the validity of this measure is unclear but would have affected both groups equally.

Functional Status

Todd et al 2017 used the Karnofsky scale index which is an assessment tool for functional impairment. A score of 50-70 on the Karnofsy Performance Status (KPS) Scale signifies inability to work but living at home and able to care for most personal needs. Score of 80-100 signifies ability to carry out normal activity and work with no assistance needed.

Post-transplant Karnofsky scale functional status scores for each of the 12 patients undergoing ECMO BTT reported as between 70 and 100 (median=90, mean=87.5). The 1-year post-transplant functional status in ECMO BTT group was not different from the non-bridged group. It was concluded that 1-year functional status was excellent in both groups. However, they highlight that this is in a select group of patients (under 65 years old, ambulatory before deterioration, no other organ dysfunction and good rehabilitation potential).

These results suggest that there is no difference between the post-transplant functional status of critically ill patients requiring ECMO BTT and less ill patients who do not require ECMO bridging support, however there is some degree of uncertainty around this. Although the study is of high quality and used a recognised and validated measure of functional status, the findings were based on relatively few patients in the ECMO BTT group who have been selected for ECMO on the basis of being of good functional status before deterioration, therefore the extent to which these results would be generalisable to patients who were less well functioning or older is questionable.

What is the clinical effectiveness and safety of ECMO or interventional lung assistance (iLA) in improving survival to transplant among patients listed to transplant?

Complications

Death on ECMO pre-transplant

Five studies report rates of death of patients while on ECMO awaiting a lung transplant, with the two best studies reporting very similar rates. Ius et al 2018 reported that 19/87 (22%) patients required ECMO BTT but died before transplantation after a median support time of 9 (4-14) days. Death was due to bleeding (cerebral n=4, other n=2), acute haemodynamic decompensation

(cardiopulmonary resuscitation n=2, right heart failure n=6), sepsis (n=4), massive haemolysis (n=1). Schechter et al 2016 reported that of the 32 patients on ECMO at time of listing, 22 (68.8%) were transplanted, whereas 6 (18.8%) either died or their condition deteriorated such that they were removed from the list. However, these data are limited by reporting only deaths for those on ECMO at the time of listing, so it is unclear how they relate to all patients who received ECMO BTT.

Three other studies report death on ECMO but are limited by small size or inclusion of older data. Todd et al 2017 reported that of a cohort of 12 patients receiving ECMO BTT none died before transplant, and Lehmann et al reported 2/15 deaths pre-transplant on ECMO. Chiumello et al 2015 reported that 10/14 studies included in the systematic review presented data on deaths while on ECMO and the proportion of the ECMO BTT cohorts that died ranged between 17% and 50% with multiple organ failure, septic shock, cardiac failure and bleeding as the most common causes. However, this study is limited by the inclusion of several older studies which assessed post-transplant outcomes on ECMO a long time ago when the technology and safety was less advanced.

There is some uncertainty as to the exact rate of mortality to expect in patients on ECMO BTT while awaiting transplant, but this is likely to be between 20% and 30%. Varying rates have been reported in the studies due to small sample sizes in several studies and differences in the level of sickness and comorbidities of the patients put on ECMO, and advances in ECMO technology and safety which will affect survival. A lack of a control group for comparison also makes it difficult to interpret this data, however it should be noted that without ECMO 100% of the patients who need it would have died.

Acute rejection and graft survival

One of the two best studies in this review reports measures of both acute rejection and longer-term graft survival. Ius et al 2018 found higher rates of acute rejection (PGD score Grade 2-3) of the graft in ECMO BTT patients than in non-bridged patients at 24 hr (37% vs 15% respectively), 48 hrs (46% vs 14%) and 72hrs (42% vs 11%), all differences significant at p=<0.001. They also followed up graft survival at 1 and 5 years and found that 90% of non-bridged and 79% of ECMO BTT patients had grafts that survived at 1 year, and 68% of non-bridged and 61% of ECMO BTT patients with grafts surviving at 5 years. These differences were not statistically significant (p=0.13) suggesting that graft survival is no worse in ECMO BTT patients. This relatively large and high-quality study suggests that acute rejection of the graft in the days immediately after transplantation is far more likely in ECMO BTT, but that in the long-term graft survival does not differ from non-bridged patients.

The second of the two best studies in this review, Schechter et al 2016, reported the proportion of patients experiencing an episode of acute rejection before discharge only. This occurred in 8.7% of non-bridged patients and 10.8% in those receiving ECMO BTT: these differences are not statistically significant.

Other studies also included rates of acute graft rejection immediately post-transplant and found there to be no significant difference between ECMO BTT and non-bridged (in agreement with Schechter et al 2016), but the studies include limitations (and none included long-term follow up of graft survival). Todd et al report

primary graft dysfunction (grade 3) at 48-72 hours post-transplant of 26% in the non-bridged group and 33% in the ECMO group with these proportions not being statistically different, but this study has a small sample size. Hayanga et al 2018 report median graft failure as 2,406 days for the non-bridged group and report 'not reached' for the ECMO BTT group without explanation of what this means which limits interpretation (although they state the difference in the graft survival between the groups is not statistically significant).

Although all studies report a trend towards higher rates of acute rejection in ECMO BTT patients in the short-term immediately post-transplant, there is some disagreement over whether this difference is statistically significant. Long-term follow up of graft survival is only reported by one study but shows that no difference between ECMO BTT and non-bridged patients at 1- and 5-years.

Post-operative ventilation

Four studies report post-operative ECMO requirement in patients, and one also reports duration of MV (see Table 1). The need for post-operative ventilation was reported by one of the two best studies included in this review. Ius et al 2018 looked at secondary ECMO requirements in patients who were on ECMO BTT and report no difference in the rate of this in ECMO BTT patients compared with non-bridged patients (4% vs 2%, p=0.18). All patients on ECMO BTT in this study were on an 'awake' ECMO strategy which did not include concurrent MV. This study did not include data on requirement for MV post-operatively.

Conversely, Hayanga et al 2018 found patients receiving ECMO BTT were significantly more likely to require post-operative ECMO but everyone in the ECMO BTT group was on concurrent MV pre-transplant. A further two smaller studies also lack consensus on whether differences in need for post-transplant ECMO in ECMO BTT and non-bridged patients was due to chance or not, with Toyoda et al 2013 finding it unlikely to be due to chance and Todd et al 2017 finding this was not the case.

Table 1: Proportion of patients requiring post-operative ECMO in each bridging strategy, % cohort

Study	**Non-bridged**	**ECMO BTT**
Hayanga et al 2018	19%	28%
Ius et al 2018	2%	4%
Todd et al 2017	2.5%	0%
Toyoda et al 2013	6%	54%

Hayanga et al 2018 also report the duration of MV required post-transplant. Patients who had ECMO BTT were more likely to be on MV for longer compared with non-bridged patients (>5 days MV in 22% non-bridged versus 67% in ECMO BTT).

Overall, there is some disagreement about whether ECMO BTT results in a greater likelihood of needing ECMO post-operatively. The different findings of the two

recent large studies (Hayanga et al 2018 and Ius et al 2018) may be due to the different ECMO BTT procedure used, i.e. with or without concurrent MV.

General short-term post-operative complications

Short-term post-operative complications were reported by five studies. The large range of different complications and the various direct and indirect measures of each make a comparison of the rates of these in ECMO BTT across studies difficult, but there were several complications which were reported as more likely to occur in ECMO BTT patients than non-bridged controls.

The two best studies in this review both report post-operative complications. The most comprehensive list of the post-operative complications seen in ECMO BTT patients compared with non-bridged patients is provided by Ius et al 2018. This studies identifies an increased risk of bleeding (indicated by need for blood products and rethoracotomy for bleeding: 21% vs 8% in ECMO BTT and non-bridged respectively), renal failure (indicated by need for dialysis: 27% vs 7%), vascular complications (10% vs 2%), need for pulsed steroid therapy (52% vs 26%), tracheostomy (34% vs 11%), longer ventilation times (median 3 days vs 1 day), and higher in hospital mortality (15% vs 5%). It should be noted that the majority (57/68) of the patients in the ECMO BTT group were on an awake ECMO strategy and so did not receive concurrent MV.

Schechter et al 2016 included only two measures of post-operative complications; episode of acute rejection before discharge (outlined above) and new onset of dialysis. The incidence of new-onset dialysis in ECMO BTT patients was higher than in non-bridged patients (13.9% vs 10.3%) but this difference was due to chance. This is a high-quality study with a relatively large cohort of patients on ECMO, however it obtained data from a national organ sharing database so is likely to have been limited in the complications it reports due to only being able to include information recorded on the database.

Other studies also identified rates of post-operative complications in ECMO BTT compared with non-bridged patients. Todd et al (2017) found some complications were more likely in patients receiving ECMO BTT than non-bridged patients, including delirium (50% vs 13.5% respectively), myopathy (83.3% vs 12.3%) and thrombotic events (50% vs 18.5%), and the need for return to the operating theatre (67% vs 16%). Blood transfusions were borderline more likely in ECMO BTT (median of 2.5 vs 1). However, this study was based on only 12 patients in the ECMO BTT group and 9/12 of these patients were sedated.

Hayanga et al 2018 also provide a detailed account of the post-operative complications for patients who received ECMO BTT compared with those who received no bridging support. There was no difference in renal insufficiency requiring dialysis (9% of non-bridged and 8% of those on ECMO BTT) and no difference in airway complications (15% of non-bridged and 18% of those on ECMO BTT). However, bleeding requiring operation was higher in the EMO BTT group compared with non-bridged (9% versus 20% respectively).

Chiumello et al 2015 looked at all the post-operative complications reported in the 14 studies included in their systematic review. The proportions of ECMO BTT

patients in each study experiencing these complications was presented but no control group data is provided which makes interpretation limited.

Overall, there is evidence that ECMO BTT is associated with some increased post-operative complications. There is relatively high certainly that the risk of bleeding is higher in ECMO BTT patients as this has been found in all the studies that report this outcome. Higher risk of renal failure is a little less consistently reported with one of the three studies including this outcome finding it to be more common in ECMO BTT and two studies finding this not to be the case. There is therefore quite a high degree of uncertainty about this outcome.

It is, however, difficult to give precise estimates of risk for each of these complications in ECMO BTT as the studies all use slightly different, indirect measures of the complications (e.g. blood transfusion vs rethoractotomy for bleeding).

Although there is some degree uncertainty due to small sample size in the single study that reports it (Todd et al 2017), there is suggestion that ECMO BTT is associated with higher risk of delirium and myopathy with around 50% and 80% of patients experiencing each of these respectively. There is slightly more certainty that thrombotic and vascular events may be an increased risk in this procedure as this was also found by a larger, more robust study (Ius et al 2018), albeit at a far lower rate (10% compared with 50% of ECMO BTT patients in Todd et al 2017).

What is the duration of pre-transplant ECMO and post-transplant hospital stay?

Duration of pre-transplant ECMO

Duration of pre-transplant ECMO was reported by five studies (Ius et al 2018, Hayanga et al 2018, Todd et al 2017, Toyoda et al 2013 and Chiumello et al 2015). One of the best studies reports a median duration of 9 days of ECMO (range 5-16) (Ius et al 2018) and the other studies report averages or medians between 4.2 days (range 0.6 – 16.5) (Todd et al 2017) and nearly 15 days (SD 15.10) (Hayanga et al 2018) in the cohort studies. There is little certainty about the exact duration of pre-transplant ECMO in these patients, but it certainly seems to be the case that durations do not tend to exceed around 16 days in the majority of patients.

Length of ITU stay

Two studies report length of ITU stay. One of the best studies, Ius et al 2018, found the median length of stay in their cohort study was 11 days (IQR 4-23 days) in ECMO BTT compared with 2 days (IQR 1-4 days) in non-bridged patients, this difference is unlikely due to chance ($p<0.001$). The systematic review by Chiumello et al 2015 identified median length of stay ranging from 15 – 47 days in patients receiving ECMO BTT but no control group data is provided and the study is limited by the inclusion of studies which are generally quite old so may be using less advanced ECMO procedures so complications and therefore ITU stays may have been longer than they would be with more modern and safe techniques. Most studies included also have relatively small sample sizes.

There is reasonable certainty that the length of post-transplant ITU stays are longer in patients who receive ECMO BTT than those who do not require bridging support. As only one recent study reports length of ITU stay the exact duration of ITU stay to be expected for an ECMO BTT patent remains unclear as it may vary centre to centre.

Length of hospital stay

Length of hospital stay was reported by six studies and generally shows a trend of longer length of stay (LOS) in ECMO BTT compared to non-bridged patients.

The two best studies in this review both report this trend in LOS but differ in whether they find this difference to be due to chance or not. Schechter et al 2016 report a median LOS of 15 days (IQR 10-24) for non-bridged patients, compared with 25 days (IQR 19-39.5) for those receiving ECMO BTT, and difference between these groups was not statistically significant. Ius et al 2018 report slightly longer median LOS for all transplanted patients; 23 days (IQR 21-28 days) for non-bridged patients and 42 days (IQR 26 – 67 days) for those on ECMO BTT. This difference was statistically significant (P<0.001).

Hayanga et al 2018 report similar LOS to Ius et al 2018 - a median of 27 days in those not receiving support and 36 days in patients on ECMO BTT – but find the difference between these groups was statistically significant. Three other smaller or more limited studies also report LOS. The small study by Todd et al report LOS of 25 days after ECMO BTT, and 13 days in non-bridged patients. This difference was unlikely due to chance. Toyoda et al 2015 report a median LOS of 46 days in ECMO BTT patients compared with 27 days in non-bridged patients but this difference is not statistically significant. Chiumello et al 2015 report a range of median LOS of 22-47 days in ECMO BTT patients in the studies included in their systematic review but no comparison group data is presented.

Overall therefore it seems that there are longer LOS in ECMO BTT than in non-bridged patents, however the exact LOS stay is not consistently reported and there is no consensus on whether differences in LOS are statistically significant between these groups.

What is the Cost effectiveness of ECMO or interventional lung assistance (iLA) in improving survival to transplant among patients listed to transplant?

Cost effectiveness of ECMO BTT

No studies addressed the cost of ECMO BTT or provided any data with which cost-effectiveness could be evaluated.

Does the evidence identify any subgroups of patients in whom clinical and cost effectiveness are different?

Awake versus sedated ECMO

One of the two best studies of outcomes in ECMO BTT (Schechter et al 2016) included some additional data that provides an indication of a subgroup of patients in whom clinical effectiveness may be better. The inclusion of additional comparison groups of patients who received MV + ECMO, and MV alone allow for assessment of the post-transplant outcomes in patients who are awake on ECMO (the ECMO only group, included in this review as ECMO BTT group) and patients who are sedated (ECMO + MV). Ideally this comparison would include equivalent awake/sedated groups in the control group where no bridging support is received, however this was not possible as this variation in care is not relevant to non-bridged patients, therefore the comparison is limited to that of awake and sedated treatment in the ECMO group only. Although the comparison of outcomes of awake and sedated patients can only be made in the ECMO group, it is nonetheless considered an important comparison to include as it may have an impact on decision making around the procedure used for ECMO BTT.

Survival at 3 years post-transplant for patients on ECMO alone was not significantly different from those not requiring support (P = 0.16), however patients requiring either MV alone or ECMO + MV had significantly worse survival compared with patients not requiring support (P < 0.0001 for both).

After adjustment with a multivariate Cox regression model, MV +/− ECMO was independently associated with worse survival compared with patients not requiring mechanical bridge (MV only: hazard ratio [HR] = 1.46; MV + ECMO = 2.26, P < 0.0001 for both), whereas ECMO alone was not (P = 0.39).

These results suggest that awake ECMO is associated with better survival than sedated ECMO which requires MV and supports the survival outcome results (above) which demonstrates that post-transplant survival for ECMO BTT is comparable to non-bridged patients. This was supported by some data in other studies; Chiumello et al 2015 who refer to one study in their systematic review which found one-year survival in ECMO BTT was significantly better in spontaneously breathing patients than mechanically ventilated ones (85% versus 50%) but no further details are given.

Conversely, Ius et al 2018 present some analysis of the differences between the awake and sedated patients in their study and report that post-transplant outcomes did not differ between patients who underwent an awake ECMO strategy and those who did not with regards to graft survival (P=0.38), patient survival (P=0.25), freedom from biopsy-confirmed rejection (P=0.53), freedom from pulsed steroid therapy (P=0.98), freedom from chronic lung allograft rejection (P=0.58), and freedom from retransplant (P=0.46). However, the number of patients on the sedated strategy was small (only 11 of the 68 patients on ECMO) so results should be treated with some caution.

Although a single study with awake versus sedated ECMO as an indirect outcome does not allow a high degree of certainty about the survival benefits of awake ECMO strategies over sedated ones, the results of the robust comparison in the high-quality Schechter et al 2016 study go some way to supporting the suggestion that patients on this ECMO strategy may demonstrate additional effectiveness of bridging over sedated strategies.

Interventional Lung Assist (iLA)

No studies provided data on iLA.

5. Discussion

The results are discussed by post-transplant outcome, or groups of outcomes if they refer to similar aspects of care or explanation. A more in-depth description of outcomes can be found in section 8 Grade of evidence table.

Survival

All studies included in this review contained post-transplant survival as an outcome, all report this at 1-year post-transplant and two include survival at 3-years, and three report it at 5-years. Although there was some variation in the exact rates of survival at each of these time points, there was very high agreement that survival is no worse in critically ill patients requiring ECMO BTT compared with less ill patients who survive to transplant without ECMO bridging support.

The published evidence suggests that 70-90% of patients who receive ECMO BTT are still alive at 1 year, around 60-80% are alive at 3 years post-transplant, and around a 65% are alive at 5-years, and this rate of survival is comparable to that of patients not receiving any bridging support.

Although the exact rates vary a little between studies, probably due to different criteria for ECMO, different case mix for transplants, procedural differences and differing use of MV, it is likely that with ever improving technologies and techniques for ECMO the survival rates increase further. The general finding that patients with ECMO BTT show comparable survival at 1-year and 5-years to patients not requiring bridging support is particularly striking in light of their degree of critical illness prior to transplantation and speaks to the overall effectiveness of ECMO BTT

Quality of life and functional status

Quality of life was only assessed by one study included in the review. Overall it was found that ECMO BTT patients achieve similar improvements in health-related quality of life after transplant as patients who do not require bridging support. The improvements are greatest in the first 6 months after transplant and then remain stable at 12 months.

Although these results give some very promising indication that ECMO BTT can confer significant benefits to quality of life, this study was relatively small and the absence of a longer duration of follow up provides no indication of the long-term impacts in these patients. It also does not cover some mental health problems that may be expected to be more common in ECMO BTT such as post-traumatic stress disorder (PTSD).

Functional status was also only assessed by one study. At 1-year post-transplant Todd et al 2017 concluded that functional status was excellent in the 12 ECMO BTT patients reviewed. A mean score of 87.5 (range 70-100) was found on the Karnofsky scale: a score of 80-100 signifies ability to carry out normal activity and work with no assistance needed. These results suggest that there is no difference between the post-transplant functional status of critically ill patients requiring ECMO

BTT and less ill patients who do not require bridging support. But the findings were based on relatively few patients in the ECMO group who have been selected for ECMO on the basis of being of good functional status before deterioration, therefore the extent to which these results would be generalisable to patients who were less well functioning or older is questionable.

Complications

Death on ECMO pre-transplant

Results for deaths on ECMO are varied and somewhat difficult to interpret. They are not reported by all studies as some only include post-transplant outcomes for patients that were successfully transplanted, and others give very limited detail about the outcome of those who do not get transplanted. Among the cohort studies that report death on ECMO, the rate ranges from 0% (Todd et al 2017) to 22% (Ius et al 2018) The systematic review by Chiumello reports mortality ranging from 17% - 50% in the studies included within it but this review generally included older studies where ECMO technology and practice may not have been as good as in more recent years. The variation seen in the mortality rates reported are likely to be due to small sample sizes in studies, differences in the level of sickness and comorbidities of the patients put on ECMO, and advances in ECMO technology and safety. The best study reporting deaths on ECMO is by Ius et al 2018 who reported that 19/87 (22%) of the patients requiring ECMO BTT died before transplantation after a median support time of 9 (4-14) days. Death was due to bleeding, acute haemodynamic decompensation, right heart failure, or massive haemolysis.

The exact rate of mortality on ECMO while awaiting transplant is difficult to determine from the studies reviewed but it is likely to be between 20% and 30%. A lack of a control group for comparison also makes it difficult to interpret this data; however, without ECMO 100% of the patients who need it would have died.

Acute rejection and graft survival

The short-term complication of acute rejection of the graft is consistently reported in the literature as more likely to occur in ECMO BTT patients than in those with no bridging support., however there is no agreement about whether this difference is significant or not. One good sized, recent study suggest that around 40% of ECMO BTT patients experience acute rejection at 24-, 48- and 72-hours post-transplant compared with just over 10% of non-bridged patients (Ius et al 2018), but another equally high-quality study found this rate to be much lower (13% on ECMO BTT vs 11% controls, Schechter et al 2016). It is unclear why these discrepancies exist as there are no obvious methodological or clinical differences that could be attributed (for example, both studies report patients receiving ECMO without MV). It may be an artefact because to the current PGD definition used in some studies (International Society for Heart and Lung Transplantation [ISHLT] Grading System) which will automatically allocate patients on ECMO to a PGD grade 3.

Long-term follow up of graft survival is only reported by one study but shows no difference between ECMO BTT and non-bridged patients at 1- and 5-years. Ius et al 2018 found that 90% of non-bridged and 79% of ECMO BTT patients had grafts that survived at 1 year, and 68% of non-bridged and 61% of ECMO BTT patients

with grafts surviving at 5 years (these differences were not statistically significant). The robust nature if this study allows a good degree of confidence in the results, however some caution is needed in the absence of support from other studies and as the authors themselves note the results may be affected by a greater number of paediatric patients in the ECMO BTT group who tend to have better graft survival outcomes.

Post-operative ventilation

There is some disagreement in the studies reviewed about whether ECMO BTT results in a greater likelihood of needing ECMO post-operatively. Excluding a very small study which did not find any ECMO BTT patients required post-operative ventilation (Todd et al 207), the studies reviewed all found a trend towards these patients requiring more ventilation, both MV (Hayanga et al 2018) and ECMO (Ius et al 2018, Hayanga et al 2018, Toyoda et al 2013), but there is no agreement over whether these differences are significant or not. One possible explanation for this is the different ECMO bridging strategies that were used in the studies, ECMO alone (Ius et al 2018) or ECMO + MV (Hyanaga et al 2018, Toyoda et al 2013). This explanation would suggest that ECMO BTT is associated with greater need for post-operative ECMO if pre-transplant MV has been given but not if an ECMO alone strategy has been adopted.

This suggests that patients who have received pre-transplant MV and ECMO may experience a slower recovery in the days immediately post-transplant and will spend longer on a ventilator in a high dependency or ITU bed, but patients who have received ECMO alone (awake ECMO) may have ventilation needs and recovery times comparable to non-bridged patients.

General short-term post-operative complications

The literature reports a number of post-operative complications seen in ECMO BTT, some of which seem to be more common in patients receiving this bridging compared to non-bridged patients. It is, however, difficult to give precise estimates of risk for each of these complications in ECMO BTT as the studies all use slightly different, indirect measures of the complications (e.g. blood transfusion vs rethoracotomy for bleeding).

Overall it seems that ECMO BTT is associated with an increased likelihood of serious post-operative complications, most clearly bleeding but also very likely delirium, myopathy and thrombotic events.

Post-transplant complications associated with ECMO BTT are not easy to assess. Nearly half of the studies did not report them at all, one only reported very limited complications as it used data from a national organ sharing database (Schechter et al 2016) so is likely to have been limited by the data recorded on the database, one was comprehensive in its reporting of complications but was based on a small sample of patients on ECMO BTT (Todd et al 2017), and the systematic review (Chiumello et al 2015) listed all the complications reported within the studies included, but provided no control group data for comparison of expected rates and the majority of studies recruited patients over ten years ago when ECMO safety was less advanced.

In summary, approximately 20 – 30% of patients will die on ECMO prior to lung transplant. Post-transplant there is no clear evidence that acute rejection is higher in ECMO BTT than non-bridged patients, and long-term follow up suggests that overall graft survival is equal. The impact of ECMO BTT on post-transplant ventilation requirements is also uncertain but the higher rates seen in ECMO BTT patients in some studies may be explained by concurrent MV use. More convincingly though, ECMO BTT is associated with higher rates of some serious complications such as bleeding, delirium, myopathy and vascular and thrombotic events. The exact magnitude of these risks is difficult to determine, but ECMO BTT is performed on very sick patients who would not survive without the bridging and subsequent lung transplant.

Duration of pre-transplant ECMO and post-transplant hospital stay

Duration of pre-transplant ECMO

The average number of days on ECMO prior to lung transplant across the studies ranged from 3.2 days to 13.7 days in the systematic review (Chiumello et al 2015) and from 4.2 days (Todd et al 2017) to nearly 15 days (Hayanga et al 2018) in the cohort studies.

This is also reflective of the range of time reported for patients within each study. Although there is little certainty about the exact duration of ECMO BTT, probably due to the different indications for ECMO at different centres and the slightly different management of transplant waiting lists, the duration does not seem to exceed around 16 days in the majority of patients. This is likely to be because once a patient is on ECMO they become a high priority on the waiting list for available donor lungs.

Length of ITU and hospital stay

The length of hospital stay for patients receiving ECMO BTT is consistently reported to be longer than that of non-bridged patients, however there is considerable variation in the exact length of stay reported both within and between centres, and there is little consensus on whether differences in length of stay between bridging strategies are likely due to chance or not. For example, Ius et al 2018 report median length of hospital stays of 23 days for non-bridged patients and 42 days for those on ECMO BTT, with this difference being unlikely due to chance, and Schechter et al 2016 report median length of stays of 15 days for non-bridged patients and 25 days for those on ECMO BTT but this difference was not statistically significant. Other studies report length of stay ranging from 13 to 27 days for non-bridged patients and 25 to 47 days for ECMO BTT patients.

The length of ITU stay was less frequently reported and only one study compared length of stay in ECMO BTT and non-bridged patients. Ius et al 2018 found that ECMO BTT is clearly associated with longer ITU stays post-transplant than no-bridging (median of 11 days compared with 2 days) A systematic review by Chiumello et al 2015 reported medians ranging from 15 – 47 days in ITU in six of 14 studies it reviewed, but no comparison with a control group was made. This systematic review included mostly older studies that may have involved less

developed ECMO technology and strategies which may have affected recovery speed. There was also some suggestion from the systematic review (Chiumello et al 2015) that the use of non-invasive ventilation strategies or awake ECMO during was associated with shorter ITU stays than invasive methods, but these were due to chance.

Overall, there is a general trend towards the reporting of longer hospital and ITU stays in patients receiving ECMO BTT but big variability within studies and between studies makes it difficult to identify the exact magnitude of difference or indeed be clear about whether any differences are significant or not. Nonetheless, It is unlikely to be surprising that patients on EMCO BTT have a longer hospital and ITU stay given that they tend to be critically ill patients with higher care needs to start with. Many of them will also have been bedbound at the time of ECMO initiation (e.g. Todd et al 2017) so prolonged recovery was anticipated. Recovery time and rehabilitation potential will be affected by many factors, including acuity of illness, ECMO duration, immobility and sedation. Although patients requiring ECMO will always be critically sick, it may be the case that a move towards awake ECMO strategies results in a reduction in the recovery period and length of stay.

Awake versus sedated ECMO

Several studies included a mix of awake and sedated ECMO patients but only one study included a comprehensive comparison of patients on these two strategies (Schechter et al 2016). This study found post-transplant survival at 3-years for patients on ECMO alone was no different from those not requiring any bridging support, but patients requiring either MV alone or ECMO plus MV had significantly worse survival compared with patients not requiring support.

In summary, there is evidence that awake ECMO offers a survival advantage over sedated strategies with concurrent MV and may also be associated with lower ventilation requirements post-operatively. However, this evidence is limited to only one study in this review, albeit a high quality one, and would benefit from further research.

Strengths and limitations

This review includes eight studies, seven of which are cohort studies (seven retrospective and one prospective (Kolaitis et al 2018)) and one systematic review (Chiumello et al 2015. They all include direct outcomes that are mainly defined by objective measures which mean they are not subject to measurement or reporting bias.

However, there are several limitations of the studies included. Most are single centre studies which may limit generalisability to other centres as case mix, clinical procedures and algorithms of care may be different. Nonetheless, some of the trends in post-transplant outcomes, such as survival, have been reported consistently across studies.

One of the most notable sources of heterogeneity in the studies is the ECMO strategy used in the ECMO BTT group, i.e. ECMO alone (awake ECMO), or ECMO with MV (sedated ECMO) or a mixture of the two in the cohort. Given that there is some evidence that outcomes such as survival and complications may be affected

by ECMO strategy used, some caution when trying to combine or interpret results is needed.

Some of the studies had small numbers of participants, particularly in the ECMO BTT group, which makes interpretation of the results difficult as it increases the risk of type 1 and type 2 errors (over or underestimating the causal inference). Although this could have potentially serious consequences, it is unlikely to be a major problem in this review as there are sufficient studies included with larger sample sizes to support the results and conclusions. Some studies include patients who received ECMO over ten years ago when technology and expertise was not so good, but again, sufficient high-quality recent studies are included to ensure this is not a source of confounding.

Due to small numbers of patients undergoing ECMO BTT many of the studies recruited patient data over long periods of time which may subject the results to a learning curve bias as the centre becomes more proficient and expert at the clinical and surgical procedures. The studies have not adjusted for effects of contemporaneous improvements in anaesthesia, pharmaceutical, or intensive care practice. This has not been accounted for in any of the studies and the magnitude of this limitation is therefore not known.

Observational studies have a number of disadvantages over randomised studies. The fact that the majority of the studies were retrospective could have introduced an element of selection bias at enrolment (with the choice to include only those patients with certain characteristics or outcomes), but all state that consecutive cases of lung transplant were included which should minimise this bias. The retrospective review of hospital records to obtain data can also provide limitations as records may be incomplete, difficult to interpret and not include information on potential confounders. In the majority of studies, the outcome data only includes patients who survive to transplant (only a couple report brief intention to treat results), and this may introduce a selection bias.

One of the fundamental limitations of this review is the absence of randomised control studies. As outlined in the introduction, studies of this type are not ethical or practical in this situation. However, there is good confidence that the controlled cohort studies included in this review (with the addition of one systematic review) have provided a reasonably robust comparison of post-transplant outcomes of ECMO BTT with an adequate control group to allow inference about the level of clinical effectiveness and safety of this procedure.

Summary of main findings

Post-transplant survival is shown with good certainty to be equal to non-bridged patients and is likely to be around 70-90% at 1-year and 65% at 5-years. Although less certainty, long-term graft survival has also been shown to be equal. Patients on ECMO BTT appear to achieve the same level of quality of life and functional status as those not undergoing this support, although the level of evidence for this is not as strong as they have been less frequently reported as outcomes.

However, the evidence convincingly indicates that ECMO BTT is associated with a higher incidence of some serious complications including bleeding, delirium, myopathy and vascular and thrombotic events. Other complications such as acute graft rejection and post-operative ventilation requirements may also be at an

increased risk in these patients, but the evidence is less certain. Similarly, ECMO BTT is associated with longer ITU stays and possibly also longer hospital stays overall, although there is less certainty about the exact duration of these and whether they are truly different from non-bridged patients. Being on ECMO is associated with a risk of death pre-transplant, 20 – 30% of patients put on ECMO will die before transplant.

There is evidence, albeit from a single study using an indirect measure of outcome, that an adoption of an awake ECMO strategy offers a survival advantage over sedated strategies which use concurrent MV. This finding potentially has significant impact on the choice of patient and ECMO strategy selected for ECMO BTT to optimise post-transplant outcomes and therefore warrants further research.

Overall, this evidence review has indicated that post-transplant outcomes (including survival) are no worse in critically ill patients requiring ECMO compared with less ill patients who survive to transplant without ECMO bridging support. Short-term complications after transplant are greater in ECMO BTT and around 20 – 30% of those on ECMO will die before transplant.

6. Conclusion

Lung transplantation is routinely performed for selected patients with respiratory failure. However approximately 25% of patients on the UK waiting list die before a suitable donor becomes available or are removed from the waiting list due to deteriorating health rendering lung transplantation futile and inappropriate. MV has traditionally been used to support these patients with the aim of bridging them to transplant but ECMO may provide a superior alternative.

This evidence review has indicated that post-transplant outcomes (including survival) are no worse in critically ill patients requiring ECMO BTT compared with less ill patients who survive to transplant without ECMO bridging support. Short-term complications after transplant are greater in ECMO BTT and 20 – 30% of those put on ECMO will die before transplant.

In light of the fact that patients who need ECMO are critically ill and have very little chance of survival without ECMO BTT, the finding of equivalent post-transplant outcomes to patients who receive no bridging support provides evidence for the use for ECMO BTT, despite the potential increased risk of complications and high pre-transplant mortality. Furthermore, the suggestion that use of an awake ECMO strategy offers a post-transplant survival advantage over sedated strategies which use concurrent MV warrants consideration of adopting this approach in clinical practice.

7. Evidence Summary Table

<table>
<tr><th colspan="7">Use of Intervention ECMO versus no ECMO as Bridge to Lung Transplant</th></tr>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Intervention</th><th>Outcome measure type</th><th>Outcome measures and Results

(Columns combined from report template)</th><th>Applicability and Quality of Evidence Score

(Columns combined from report template)</th><th>Critical Appraisal Summary</th></tr>
<tr>
<td>Hayanga et al 2018</td>
<td>P1 - Retrospective cohort study</td>
<td>Total population of patients who underwent primary lung transplantation between 2008 and 2015 (N=826) Split into three cohorts: Non-Bridged (n =29), MV only BTT (n = 48), ECMO + MV BTT (n = 49).

Single centre: Pittsburgh Medical Center, USA</td>
<td>Outcomes reported here for Non-Bridged and ECMO + MV (ECMO BTT) groups.

To analyse outcomes, 194/729 patients in the control group were propensity matched by age and diagnostic category to those in ECMO BTT group (2:1)</td>
<td>Primary CE</td>
<td>Overall survival

Median survival (days)
<table><tr><td>Non-bridged</td><td>ECMO BTT</td></tr><tr><td>2437</td><td>Not reached</td></tr></table>P values: Non-bridged Vs ECMO BTT =0.4693

Survival Probability
<table><tr><td></td><td>Non-Bridged</td><td>ECMO BTT</td></tr><tr><td>30-day</td><td>0.974 (0.939-0.989)</td><td>0.939 (0.822-0.980)</td></tr><tr><td>90-day</td><td>0.949 (0.906-0.972)</td><td>0.898 (0.772-0.956)</td></tr><tr><td>1 year</td><td>0.839 (0.779-0.884)</td><td>0.815 (0.675-0.899)</td></tr><tr><td>3 years</td><td>0.731 (0.659-0.789)</td><td>0.769 (0.621-0.865)</td></tr><tr><td>5 years</td><td>0.588 (0.502-0.664)</td><td>0.656 (0.477-0.787)</td></tr></table>Survival conditioned on surviving to 1 year, median
<table><tr><td>Non-bridged</td><td>ECMO BTT</td></tr><tr><td>2858</td><td>Not reached</td></tr></table>P values: Non-bridged Vs ECMO BTT p=0.1559</td>
<td>Applicability: Direct. Looks at outcomes of patients bridged to lung transplant with ECMO compared with patients not requiring bridging support.

Quality: 7/10 total

Aims and design clearly stated 2/2: purpose of study clearly stated as being to evaluate pre-transplantation MV with and without ECMO. Primary and secondary outcomes pre-determined.

Design appropriate: 2/2: retrospective cohort study appropriate.

Methods clearly described: 1/2: Not described fully in this paper but references full methods described elsewhere.

Data adequate for authors' interpretation: 1/2: Clear objective outcomes used but unclear what 'not reached' means in results presented</td>
<td>Positives:

All consecutive patients undergoing lung transplant during the defined period included so selection bias minimal.

Relatively large numbers in ECMO BTT group provide power for statistical analysis.

Propensity matching of controls used to make groups more similar for comparison.

Outcomes are objective.

Survival data for 5 years included.

Negatives:

Not clear if MV and ECMO were used concurrently or sequentially and no detail about level of sedation.

Patients in ECMO BTT group were more likely to have bilateral lung transplants compared with the non-bridged group which may have impacted survival and complications data.

Unclear if time on ventilator includes time on ECMO or just time on MV, and whether it is pre-op or pre- and post-op.</td>
</tr>
</table>

<table>
<tr>
<td></td><td></td><td></td><td></td>
<td>Secondary CE</td>
<td>Duration of ECMO
Time on ECMO pre-transplant in ECMO BTT patients reported as a mean of 14.58 (SD 15.10).</td>
<td rowspan="4">and how this contributes to conclusions

Results generalizable:1/2: generalisable to population receiving ECMO with concurrent MV only, no inclusion of patients on ECMO alone for comparison.</td>
<td rowspan="4">Relatively long period of recruitment of participants could mean there is learning curve bias or confounding effect of changing ECMO technology or practice, this is not considered by the authors.</td>
</tr>
<tr>
<td></td><td></td><td></td><td></td>
<td>Secondary CE</td>
<td>Post-operative ventilation

Ventilation postoperative, n (%)
<table>
<tr><td></td><td>Non-bridged</td><td>ECMO BTT</td></tr>
<tr><td>MV <48h</td><td>119 (61.66)</td><td>2 (4.08)</td></tr>
<tr><td>MV 48h – 5days</td><td>31 (67.35)</td><td>14 (28.57)</td></tr>
<tr><td>MV >5 days</td><td>43 (22.28)</td><td>33 (67.35)</td></tr>
<tr><td>ECMO +MV</td><td>19 (9.79)</td><td>28 (57.14)</td></tr>
</table>
<48h P value: Non-Bridged Vs ECMO BTT p=<0.001

48h – 5 days P value: Non-Bridged Vs ECMO BTT p=0.044

>5 days P value: Non-Bridged Vs ECMO BTT p=0.184, MV Vs MV & ECMO p=0.215

ECMO + MV P value: Non-Bridged Vs ECMO BTT p=<0.001</td>
</tr>
<tr>
<td></td><td></td><td></td><td></td>
<td>Secondary CE</td>
<td>Length of hospital stay
Hospital stay (days), median (IQR)
<table>
<tr><td>Non-Bridged</td><td>ECMO BTT</td></tr>
<tr><td>27 (21)</td><td>36 (21)</td></tr>
</table>
P value: Non-Bridged Vs ECMO BTT p=0.0012</td>
</tr>
<tr>
<td></td><td></td><td></td><td></td>
<td>Secondary safety</td>
<td>Incidence of complications
Graft survival (days), median
<table>
<tr><td>Non-Bridged</td><td>ECMO BTT</td></tr>
</table></td>
</tr>
</table>

2406	Not reached

P value: Non-bridged Vs ECMO BTT p=0.5358

Retransplant, n (%)

Non-Bridged	ECMO BTT
7 (3.61)	1 (2.04)

P value: Non-bridged Vs ECMO BTT p=1.00

Time to retransplantation (days), median (IQR)

Non-Bridged	ECMO BTT
129 (572)	1490

P value: Non-bridged Vs ECMO BTT p=0.285

Acute rejection grade, n (%)

Grade	Non-Bridged	ECMO BTT
[0,1]	108 (57.75)	31 (68.89)
[1,2]	31 (16.58)	7 (15.56)
[2,3]	29 (15.51)	4 (8.89)
[3,4]	19 (10.16)	3 (6.67)

Acute rejection overall P value: Non-bridged ECMO BTT p=0.555

[0,1] P value: Non-bridged Vs ECMO BTT p=0.181

[1,2] P value: Non-bridged Vs ECMO BTT p=1.00

[2,3] P value: Non-bridged Vs ECMO BTT p=0.344

[3,4] P value: Non-bridged Vs ECMO BTT p=0.582

Renal insufficiency on dialysis, n (%)

Non-Bridged	ECMO BTT
18 (9.28)	4 (8.16)

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P value: Non-bridged Vs ECMO BTT p=1.00

Bleeding requiring operation, n (%)
<table><tr><td>Non-Bridged</td><td>ECMO BTT</td></tr><tr><td>16 (8.25)</td><td>10 (20.41)</td></tr></table>P value: Non-bridged Vs ECMO BTT p=0.014
Airway complication, n (%)
<table><tr><td>Non-Bridged</td><td>ECMO BTT</td></tr><tr><td>29 (14.95)</td><td>9 (18.37)</td></tr></table>P value: Non-bridged Vs ECMO BTT p=0.556</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Todd et al 2017</td>
<td>P1 – retrospective cohort study</td>
<td>Total patients undergoing lung transplant during 2015 (N=93) split into 2 cohorts:

ECMO BTT (n=12), Non-bridged (n=81)

Single centre: Norton Thoractic Institute, Arizona, USA</td>
<td>Outcomes reported here for both groups; ECMO BTT and non-bridged.

3/12 patients in ECMO BTT group were awake and 9/12 were sedated</td>
<td>Primary CE</td>
<td>Length of stay

Length of hospital stay, median (IQR)
<table><tr><td>variable</td><td>Non-Bridged</td><td>ECMO BTT</td><td>P value</td></tr><tr><td>Total LOS, median (IQR)</td><td>15 (11-26)</td><td>39 (32.5-50.5)</td><td><.001</td></tr><tr><td>Post-transplant LOS, median (IQR)</td><td>13 (10-17)</td><td>25 (18-31)</td><td><.001</td></tr></table></td>
<td rowspan="3">Applicability: Direct. Compares patients bridged to transplant with ECMO and those not requiring bridging.

Quality: 8/10

Aims and design clearly stated 1/2: Aims clearly stated as comparing the outcomes of all patients who received ECMO BTT with those of patients who were not bridged during the same period. Outcomes predetermined but no reference to whether primary or secondary.

Design appropriate 2/2: Retrospective cohort study appropriate.

Methods clearly described 2/2: Methods of study and procedure clearly described.

Data adequate for authors' interpretation 1/2: Generally yes, but unable to find 90 day survival results and the</td>
<td rowspan="3">Positives:

All consecutive patients undergoing lung transplant during study period included so selection bias minimal.

Outcomes are objective and therefore prone to minimal measurement bias and test for functional status is a validated tool.

Patients recruited from a single year so learning curve bias or confounding effects of changing ECMO technology and practice is minimal.

Negatives:

Small sample size, particularly in ECMO BTT group (n=12) may increase risk of type 2 error and make interpretation of results difficult.

Although study states that 3/12 patients were awake on ECMO, outcomes are not presented in relation to this so no inferences or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primary CE</td>
<td>Duration of pre-transplant ECMO

Mean duration 103.6 hours (range 16 – 395 hours)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Primary CE</td>
<td>Survival

Pre-transplant survival:

All patients on ECMO BTT survived to transplant

Post-transplant survival:</td>
</tr>
</table>

					variable	Non-Bridged	ECMO BTT	P value	functional status data of ECMO BTT patients lack comparison data from control group. Results generalizable 2/2: Patient and procedure characteristics are generalisable to most ECMO BTT.	conclusions about the impact of the ECMO strategy can be drawn. Functional status scores reported for ECMO BTT patients but not for non-bridged patients so no comparison possible which therefore limits the interpretation of the magnitude of scores in ECMO BTT group.
					30-d mortality, n (%)	1 (1.2)	0 (0)	>.99		
					Survival at 1 y, n (%)	73/80 (91.3)	12/12 (100)	1.0		
				Primary CE	**Functional status at one year** Post-transplant Karnofsky scale functional status scores for each of the 12 patients undergoing ECMO BTT reported as between 70 and 100 (median=90, mean=87.5). The 1-year functional status in ECMO BTT group was not significantly different from the non-ECMO group (p=0.74) Score of 50-70 on the Karnofsy Performance Status (KPS) Scale signifies inability to work but living at home and able to care for most personal needs. Score of 80-100 signifies ability to carry out normal activity and work with no assistance needed.					
				Secondary Safety	**postoperative complications**					
					variable	Non-Bridged (n=81)	ECMO BTT (n=12)	P value		
					Primary Graft Dysfunction (PGD) grade 3 at 48-72 h	21 (25.9)	4 (33.3)	0.72		
					ECMO for PGD	2 (2.5)	0 (0)	>.99		
					Postoperative PRBC transfusion, median (IQR)	1 (0-2)	2.5 (0.5-8)	.05		
					Return to OR, n (%)	13 (16.1)	8 (66.7)	.001		

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<table>
<tr><td>Reintubation post-transplant, n (%)</td><td>5 (6.2)</td><td>1 (9.3)</td><td>.57</td></tr>
<tr><td>Tracheostomy post-transplant, n (%)</td><td>6 (7.4)</td><td>2 (16.7)</td><td>.27</td></tr>
<tr><td>Pneumonia, n (%)</td><td>9 (11.1)</td><td>2 (16.7)</td><td>.63</td></tr>
<tr><td>Post-transplant bronchoscopies during hospital stay, median (IQR)</td><td>3 (2-4)</td><td>3.5 (3-6)</td><td>.04</td></tr>
<tr><td>Delirium, n (%)</td><td>11 (13.5)</td><td>6 (50)</td><td>.01</td></tr>
<tr><td>Myopathy, n (%)</td><td>10 (12.3)</td><td>10 (83.3)</td><td><.001</td></tr>
<tr><td>Thrombotic event, n (%)</td><td>15 (18.5)</td><td>6 (50)</td><td>.03</td></tr>
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<tr>
<td>Kolaitis et al 2018</td>
<td>P1 – Prospective cohort study</td>
<td>Three cohorts recruited 2010 - 2017: ECMO BTT (N=17), patients hospitalised but not on ECMO (N=48), patients called in for transplant as outpatients (N=124)

Single centre: San Francisco, USA</td>
<td>Outcomes reported here for ECMO BTT cohort and for patients called in for transplant from home (non-bridged).

Patients over 65 years old excluded</td>
<td>Primary CE</td>
<td>
Health-related Quality of Life (HRQL)
Measured with:

SF12-PCS (Short Form 12–Physical Component Score), range 0 to 100
SF12-MCS (Short Form 12–Mental Component Score), range 0 to 100
AQ20R (Airways Questionnaire 20–Revised), range 0 to 20, reverse-coded for analysis
EQ5D (EuroQoL 5D), range -1.11 to 1
GDS (Geriatric Depression Scale), range 0 to 15

Effect estimates for change in HRQL over time from before to 6 months after transplant, mean effect estimates with 95% CI
<table>
<tr><td>HRQL measure</td><td>ECMO BTT</td><td>Non-Bridged</td><td>P value</td></tr>
</table>
</td>
<td>
Applicability: Direct. Looks at outcomes of patients bridged to lung transplant with ECMO compared to those not requiring bridging support.

Quality: 9/10

Aims and design clearly stated 2/2: Aims clearly stated as seeking to evaluate whether the impact of lung transplantation on HRQL within first postoperative year was different in patients on ECMO BTT compared with those who were not.

Design appropriate 2/2: prospective cohort study completely appropriate.
</td>
<td>
Positives:

Included all patients in the centre receiving ECMO BTT during study period with participants prospectively identified so selection bias minimised.

Several measures of health-related quality of life used to get comprehensive picture.

Sensitivity analysis with imputed data performed to assess impact of missing data.

Negatives:

Some loss to follow up with survey completion which led to missing data - overall the number of missing surveys was 104 of 742 potential
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<table>
<tr><td>SF12-PCS</td><td>16.78 (10.65-21.91)</td><td>20.78 (18.50-23.07)</td><td>.27</td></tr>
<tr><td>SF12-MCS</td><td>8.78 (3.31-14.26)</td><td>4.48 (2.47-6.49)</td><td>.01</td></tr>
<tr><td>AQ20R</td><td>10.76 (8.57-12.96)</td><td>9.76 (8.96-10.56)</td><td>.59</td></tr>
<tr><td>EQ5D</td><td>0.31 (0.20-0.42)</td><td>0.17 (0.13-0.21)</td><td>.001</td></tr>
<tr><td>GDS</td><td>4.81 (3.15-6.48)</td><td>3.54 (2.94-4.14)</td><td>.09</td></tr>
</table>
(Note that P values include a third group (inpatients but not ECMO) in the test of difference).

Secondary CE

Overall Survival at 1 year
Overall survival at 1 year was 97% and was similar in all groups (p=.44). One patient in the ECMO BTT group (1/17; 6%), and 2 patients in the non-bridged group (2/124; 2%) died within the first year.
</td>
<td>Methods clearly described 2/2: Study methods and clinical details clearly described, good detail on loss to follow up.

Data adequate for authors' interpretation 2/2: Clear and comprehensive data on HRQL supports interpretation and conclusions.

Results generalizable 1/2: Generalisable in so far as likely to represent a population of patients undergoing ECMO BTT, but no mention of what psychiatric or psychological support these patients are given at the centre. Only patients <65 years old included so may not generalise to older patients.</td>
<td>timepoints (14%). As authors acknowledge, informative missingness could therefore have impacted results. This was minimised by imputing missing data and performing sensitivity analysis.

Relatively small number in ECMO BTT (n=17) may increase risk of type 2 error and make interpretation of statistical analyses difficult.

Only followed up for 1 year so no detail on long term effects on HRQL are provided by this study.

Very few details of ECMO procedure given so generalisability to other populations is limited, e.g. no details of level of sedation of patients on ECMO so no inferences can be made about impact of this, and no details of duration of ECMO given so impact of this cannot be inferred.

Only includes those who underwent transplant. As no data on patients who died on ECMO while awaiting transplant are included which may skew results.

Depression was measured with the geriatric depression score which is well validated for people >65 years old but may be less so for those <65. However, this would affect both groups.</td>
</tr>
<tr>
<td>Schechter et al 2016</td>
<td>P1 – retrospective cohort study</td>
<td>Total population of all adults with lung transplantation 2005 – 2013 (N=12,403) in four cohorts: ECMO only BTT (n=65),</td>
<td>Outcomes reported here for the cohort of patients receiving ECMO only BTT (ECMO BTT) and those receiving no</td>
<td>Primary CE</td>
<td>
Survival
Cumulative survival, %:
<table>
<tr><td></td><td>Non-Bridged</td><td>ECMO BTT</td></tr>
<tr><td>6 months</td><td>89.4%</td><td>75.2%</td></tr>
<tr><td>1 year</td><td>84.2%</td><td>70.4%</td></tr>
<tr><td>3 years</td><td>67%</td><td>64.5%</td></tr>
</table>
</td>
<td>Applicability: Direct. Compares outcomes of lung transplants using different bridging strategies including ECMO, with patients who did not require bridging support.

Quality: 10/10</td>
<td>Positives:

All isolated lung transplants on register included so selection bias is minimal.

Relatively large sample size means that statistical analyses can be interpreted with some confidence and risk of type 2 errors is small.</td>
</tr>
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<td>MV only BTT (n=612), ECMO + MV BTT (n=119), no bridging support (n=11,607).

Data obtained from the United Network of Organ Sharing database</td>
<td>bridging (non-bridged). support (non-bridged).</td>
<td></td>
<td>Mid-term survival for patients on ECMO BTT was not significantly different from non-bridged patients (P = 0.16).</td>
<td rowspan="4">Aims and design clearly stated 2/2: Aims clearly stated as evaluating the effect of non-intubated ECMO BTT on survival after lung transplantation. Primary and Secondary outcomes predetermined and clearly detailed.

Design appropriate 2/2: retrospective cohort study completely appropriate

Methods clearly described 2/2: Yes, study methods clearly described.

Data adequate for authors' interpretation 2/2: Authors make appropriate conclusions about the survival benefits of ECMO BTT alone versus other bridging strategies and no bridging.

Results generalizable 2/2: Use of data from large organ sharing database and comparison of several bridging strategies make results highly generalisable.</td>
<td rowspan="4">Provides data for ECMO alone compared with ECMO + MV which therefore gives evidence relative impacts of each of these bridging strategies (in comparison with several of the other studies which include these as one cohort).

Negatives:

Only outcomes available on the registry could be included so limited results of effectiveness and safety presented.

Lack of detail on the level of mobility or ambulation of the patients receiving ECMO BTT (beyond stating that they are awake) limit the clinical interpretation of the outcomes of this strategy.

Data on deaths on waiting list appears to include only those on that method of support at time of listing so it is unclear how this relates to the whole cohort (e.g. are some patients changing strategy after time of listing?).

No details of duration of ECMO or other support in patients while awaiting transplant is provided and this could be a confounding factor in the outcome results.</td>
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<tr>
<td></td>
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<td></td>
<td>Secondary CE</td>
<td>length of post-transplant hospital stay

length of stay, median (IQR)

<table>
<tr><td>Non-Bridged (n=11607)</td><td>ECMO BTT (n=65)</td></tr>
<tr><td>15 (10-24)</td><td>25 (19-39.5)</td></tr>
</table>
p-value for difference in length of stay by between bridging strategy p=0.076</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Secondary Safety</td>
<td>Post-transplant complications

Episode of acute rejection before discharge, n (%):

<table>
<tr><td>Non-Bridged (n=11607)</td><td>ECMO BTT (n=65)</td></tr>
<tr><td>997 (8.7%)</td><td>7 (10.8%)</td></tr>
</table>
P (bridging strategy)=0.21

New onset of dialysis, n (%):

<table>
<tr><td>Non-Bridged (n=11607)</td><td>ECMO BTT (n=65)</td></tr>
<tr><td>552 (4.8%)</td><td>9 (13.9%)</td></tr>
</table>
P (bridging strategy)=<0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Secondary Safety</td>
<td>Deaths on waiting list pre-transplant

Of the 32 patients on ECMO at time of listing, 22 (68.8%) were transplanted, whereas 6 (18.8%) either</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>died or their condition deteriorated such that they were removed from the list.</td><td></td><td></td></tr>
<tr><td>Lehman et al 2015</td><td>P1 – Retrospective cohort study</td><td>Total population of all patients undergoing lung transplantation 2002-2011 (N=143) in two cohorts: Mechanical lung assist (ECMO or extracorporeal lung assist (ECLA)) (n=13), and non-bridged (n=130)

Single centre: Leipzig, Germany</td><td>Outcomes reported here for both cohorts; patients on ECMO or ECLA (ECMO BTT group), and non-bridged group.

Of the total population: 74/143 patients had a single lung transplant and 69/143 underwent bilateral lung transplants

Of those receiving MLA: 12/13 received ECMO and 1/13 received ECLA.

5/13 patients on ECMO BTT were awake and extubated.</td><td>Primary CE</td><td>Survival

<table><tr><td></td><td>30 day</td><td>90 day</td><td>1 year</td><td>5 year</td></tr><tr><td>Non-Bridged</td><td>95±1.8 %</td><td>90±2.6 %</td><td>71±4%</td><td>52±5.7 %</td></tr><tr><td>ECMO BTT</td><td>85±1%</td><td>77±1.2 %</td><td>68±1.3 %</td><td>34±1.8 %</td></tr></table>P value for difference between non-bridged and ECMO BT p-=0.281</td><td rowspan="3">Applicability: Direct. Compares patients bridged to transplant with ECMO with those not receiving bridging support.

Quality: 6/10

Aims and design clearly stated 1/2: Aims clearly stated as conducting a study to compare survival in lung transplant patients with and without preoperative MLA support. Design clearly outlined but outcomes of interest not specified.

Design appropriate 2/2: A retrospective cohort design is appropriate.

Methods clearly described 1/2: generally described adequately but very little detail about the outcome variables is provided.

Data adequate for authors' interpretation 1/2: Data presented support conclusion that MLA has no impact on long term survival but sample is small and variable characteristics of lung transplant and MLA may be affecting results.

Results generalizable 1/2: Results include single and bilateral lung transplants and some concomitant heart</td><td rowspan="3">Positives:

Study includes all consecutive lung transplant patients during study time so selection bias is minimal.

Follow up was 100% complete and ranged from 0.5 to 11.4 years.

5-year survival presented which provides good data on long-term effectiveness of ECMO BTT.

Negatives:

Small sample size, particularly in ECMO BTT group (n=13) make interpretation of statistical analyses difficult and increase risk of type 2 error.

heterogeneity in lung transplant procedure and MLA procedure make interpretation and generalising of results difficult. For example, 6 patients from the non-bridged group and 8 from the ECMO BTT group were preoperatively on MV which may confound the results but data presented do not account for this, and no details given about effect of single vs bilateral transplant.

Only one patient in ECMO BTT group reported as being on ECLA rather than ECMO but comparison data for this is not presented no unclear how this procedure may have affected outcomes.

Very few outcome measures presented as comparison between the ECMO BTT and the non-bridged group so interpretation of the</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Secondary Safety</td><td>Duration of pre-transplant ECMO

Mean duration on ECMO = 146 ±404 hours (range = 6 hours – 30 days)</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Secondary Safety</td><td>Deaths while on ECMO pre-transplant

2/15 patients died on ECMO while on the waiting list due to multiorgan failure or brain haemorrhage.</td></tr>
</table>

						surgery, and ECMO procedure is variable (e.g. some patients sedated and some awake) so some difficulty generalising results occurs from this.	magnitude of outcomes in ECMO BTT patients is limited. No data presented to indicate if there were any deaths on ECMO while awaiting transplant or not
Chiumello et al 2015	S1 – systematic review	14 studies included, all retrospective case series studies with total N=441 enrolled patients who underwent ECMO BTT	Outcomes reported here for the only group presented in systematic review – ECMO BTT group. Due to substantial heterogeneity across studies a meta-analysis was not attempted	Primary CE	**Survival** 14/14 studies reported 1-year survival. In five studies it ranged from 50% to 70%, in four 70% to 90% and in two up to 90% one-year survival was significantly better in spontaneously breathing patients than mechanically ventilated ones (85% versus 50%) or when the ECMO bridge duration was shorter than 14 days (82% versus 29%).	**Applicability:** Direct. Included studies with at least 10 patients on ECMO bridging. **Quality**: 8/10 Aims and design clearly stated 2/2: clearly stated as a systematic review to assess the current evidence on the use of ECMO BTT in patients with advanced respiratory failure awaiting lung transplant. Design appropriate 2/2: Systematic review completely appropriate. Methods clearly described 1/2: systematic review methods and quality assessment clearly described, but outcomes not specified or described in advance. Data adequate for authors' interpretation 2/2: Authors are appropriately cautious about the conclusions that can be drawn from a heterogeneous set of case series studies. Results generalizable 1/2: results do refer to patients on ECMO as BTT, but due to old studies and heterogeneity of them some caution is needed when generalising.	**Positives:** Search included all major databases with broad search strategy so should include all relevant studies therefore inclusion bias likely to be minimal. References and abstracts reviewed by 3 independent reviewers, methodology and quality assessed by 2 independent reviewers. Review of several studies together make the conclusions more reliable than if only a single study was used. **Negatives:** Studies included were case series with no control groups so confounding factors are not controlled for within each study. It is also difficult to make inference about the magnitude of outcomes observed or discern whether or not survival/risk actually from differs from patients not on ECMO BTT. Studies included are all relatively old (published 2010 – 2013) and may therefore reflect survival and risks associated with older, less developed ECMO technology and practice. Sample sizes in studies were relatively small (11 – 122 patients) which may have resulted in imprecision in the data and a lack of
				Primary CE	**Mortality on ECMO pre-transplant** Reported in 10/14 studies and ranged between 17% and 50% with multiple organ failure, septic shock, cardiac failure, and bleeding as most common causes		
				Secondary CE	**Length of stay** ICU stay: reported in 6/14 studies and medians ranged from 15 – 47 days in ECMO BTT. Hospital length stays: reported in 9/14 studies and medians ranged from 22 – 47 days in ECMO BTT.		
				Secondary safety	**Post-operative complications in ECMO BTT patients** Respiratory complications: Post-op graft dysfunction requiring Post-Ltx ECMO: 4/14 studies (20% - 54%) Post-op graft dysfunction 72 hours 3rd grade: 3/14 studies (15%-36%) Tracheostomy: 4/14 studies (27% - 77%) Bronchopleural fistula: 2/14 studies (8%- 14%) Open chest management: 2/14 studies (8%-50%) Acute rejection: 2/14 studies (15%- 28%)		

					Acute kidney injury: 2/14 studies (12% - 35%) Renal replacement therapy: 7/14 studies (12% - 54%) Infective complications: Pneumonia: 1/14 studies (52%) Sepsis: 3/14 studies (14% - 23%) Haemorrhagic complications: GI bleeding: 1/14 studies (5%) Bleeding from femoral artery: 1/14 studies (5%) Re-op. for bleeding: 5/14 studies (15%-36%) Haemorrhage: 2/14 studies (31%- 35%) Massive haemoptysis: 1/14 studies (15%) Neurological complications: Cerebral haemorrhage: 1/14 studies (5%) Stroke: 1/14 studies (8%) Ischemia thoracic spinal cord: 1/14 studies (3%) Digital ischemia: 2/14 studies (14%-17%)		adequate statistical power within studies. There were substantial differences in the inclusion criteria for patients, ECMO program times, and ECMO support technologies therefore it is not possible to exclude a possible confounding role of some important procedural aspects. As the authors acknowledge, there was substantial heterogeneity across studies a meta-analysis was not attempted because it would not have yielded clinically meaningful results.
				Secondary Safety	**Duration on ECMO pre-transplant** Time on ECMO pre-transplant ranged in the studies from a median of 3.2 days to 16 days.		
Toyoda et al 2013	P1 – Retrospective cohort study	Total population of patients transplanted 2005 - 2011	Outcomes reported here for both cohorts; ECMO BTT	Primary CE	**Survival** Actuarial survival, % ECMO BTT / Non-Bridged	**Applicability:** Direct. Includes outcomes of patients undergoing ECMO BTT and non-bridged controls.	**Positives:** All consecutive patients who underwent ECMO BTT at the

		(N=715) in two cohorts: ECMO BTT (n= 24), non-bridged patients (n=691) Single centre: university of Pittsburgh Medical Centre	group and non-bridged group. 31 patients put on ECMO but 7 of these were not transplanted. 3/24 patient in ECMO BTT group had a retransplant		<table><tr><td>1 month</td><td>96%</td><td>97%</td></tr><tr><td>3 months</td><td>88%</td><td>94%</td></tr><tr><td>6 months</td><td>83%</td><td>90%</td></tr><tr><td>12 months</td><td>74%</td><td>83%</td></tr><tr><td>24 months</td><td>74%</td><td>74%</td></tr></table>Difference in survival between ECMO BTT and non-bridged group p=0.787	**Quality: 7/10** Aims and design clearly stated 1/2: Aims clearly stated as reviewing the efficacy of ECMO BTT, not including heart-lung transplantation. Outcomes not detailed. Design appropriate 2/2: Retrospective cohort study completely appropriate. Methods clearly described 1/2: methods of clinical procedure detailed well but no detail about gathering of outcome data. Data adequate for authors' interpretation 2/2: data clearly support the conclusions Results generalizable 1/2: Although results relate to patients on ECMO BTT, period of recruitment began over 10 years ago and changes in procedure may affect generalisability to survival and safety in current practice.	institution included so selection bias is minimised. **Negatives:** Relatively small sample size, particularly in ECMO BTT group may have affected precision of results (although no measure of error provided so it is not possible to discern if this is an issue). ECMO BTT group contained patients undergoing retransplants as well as first transplants which may confound the survival and safety outcomes but this has not been considered in the analysis. The long recruitment period may have introduced a learning curve bias and the inclusion of some patients who underwent ECMO over 10 years ago could be resulting in confounding from changes in ECMO technology and practice seen over this time. No details are given of the 7 patients who were on ECMO with intention to transplant but did not receive transplant. It is unclear if they died as a result of ECMO complications or failed to have a suitable donor identified. 6 of the 24 patients on ECMO BTT received cadaveric lobar transplants because a suitable donor could not be found. It is unclear how this might affect the results with regards to outcomes of these patients but as this is potentially a risky procedure it may decrease survival and increase complication estimates in this group.
				Secondary CE	**Length of stay** Median length of hospital stay was 46 days in ECMO BTT group compared with 27 in non-bridged group (p=0.16)		
				Secondary Safety	**Post-transplant complications** ECMO support was used postoperatively for primary graft dysfunction in 54% of patients in the ECMO BTT group and 6% of patients in the on-bridged group (P <.01)		
				Secondary Safety	**Duration of ECMO pre-transplantation** The duration of pre-transplant ECMO support in the ECMO BTT group was 171±242 hours (range, 2-1104 hours)		

<table>
<tr>
<td>Ius et al 2018</td>
<td>P1 – Retrospective cohort study</td>
<td>Total population of all patients undergoing transplant 2010 – 2017 (N=917) in two cohorts: patients with ECMO BTT (N=68), patients with no bridging support (N=849).

Single centre: Hannover, Germany</td>
<td>Outcomes reported here for both cohorts; ECMO BTT group and non-bridged group.

Awake ECMO strategy used in 57/68 of the ECMO BTT patients.

9/68 ECMO BTT patients and 52/849 non-ECMO BTT patients had retransplant.

11/68 patients in ECMO BTT and 53/849 patients in non-ECMO BTT were <18 years old</td>
<td>Primary CE</td>
<td>Survival
Patient survival overall, % (n)
<table>
<tr><th></th><th>ECMO BTT (n=68)</th><th>Non-Bridged (n=849)</th><th>P-value</th></tr>
<tr><td>1 year</td><td>79 (5)</td><td>90 (1)</td><td>0.095</td></tr>
<tr><td>5 years</td><td>65 (9)</td><td>71 (2)</td><td></td></tr>
</table>
Patient survival conditioned to hospital discharge, % (n)
<table>
<tr><th></th><th>ECMO BTT (n=68)</th><th>Non-Bridged (n=849)</th><th>P-value</th></tr>
<tr><td>1 year</td><td>93 (3)</td><td>95 (1)</td><td>0.97</td></tr>
<tr><td>5 years</td><td>77 (6)</td><td>75 (2)</td><td></td></tr>
</table>
</td>
<td rowspan="3">Applicability: Direct. Includes outcomes of patients undergoing ECMO BTT compared with those not receiving ECMO BTT.

Quality: 9/10

Aims and design clearly stated 2/2: Aim stated as investigating impact of ECMO BTT on graft survival at follow up. Primary and Secondary end points clearly pre-determined.

Design appropriate 2/2: Retrospective cohort study completely appropriate

Methods clearly described 2/2: study methods and clinical procedures clearly outlined.

Data adequate for authors' interpretation 1/2: mostly the data do support the conclusions, but the authors state that an awake ECMO strategy should be used when their data suggest there is no difference in outcomes between those awake and those not (although numbers in not-awake group were very small).

Results generalizable 2/2: Good confidence in generalisability due to large sample size and relatively recent recruitment of patients.</td>
<td rowspan="3">Positives:

Includes all consecutive cases of lung transplant at the centre therefore selection bias is unlikely

Relatively large sample size and number of patients receiving ECMO BTT so results are more generalisable and risk of type 2 error is not too great.

Compares awake and sedated ECMO (with MV) in results which accounts for a potentially important confounding factor in analysis of survival and safety of ECMO and provides useful data on optimal ECMO strategy.

Negatives:

As authors acknowledge, the greater number of paediatric patients in the ECMO BTT group than the non-ECMO group may have positively influenced transplant survival in the former group.

Patients who died on ECMO while awaiting transplantation were excluded form analysis. The authors explain this as being due to a desired focus on the impact of ECMO BTT. However, this could inflate survival data post-transplant and reduce the apparent complications of ECMO BTT as the sickest patients won't be considered in the analysis.</td>
</tr>
<tr>
<td>Primary CE</td>
<td>Graft survival
Graft Survival, % (n)
<table>
<tr><th></th><th>ECMO BTT (n=68)</th><th>Non-Bridged (n=849)</th><th>P-value</th></tr>
<tr><td>1 year</td><td>79 (5)</td><td>90 (1)</td><td>0.13</td></tr>
<tr><td>5 years</td><td>61 (6)</td><td>68 (2)</td><td></td></tr>
</table>
</td>
</tr>
<tr>
<td>Secondary CE</td>
<td>ICU and hospital stay
Duration of ICU and hospital stay, days (IQR)
<table>
<tr><th></th><th>ECMO BTT (n=68)</th><th>Non-Bridged (n=849)</th><th>P-value</th></tr>
<tr><td>ICU stay</td><td>11 (4-23)</td><td>2 (1-4)</td><td><0.001</td></tr>
<tr><td>Hospital stay</td><td>42 (26-67)</td><td>23 (21-28)</td><td><0.001</td></tr>
</table>
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</table>

Secondary

Safety

Post-operative complications

Median (IQR) or n (%)

	ECMO BTT (n=68)	Non-Bridged (n=849)	P-value
PGD 2 or 3 at 24h	25 (37)	125 (15)	<0.001
PGD 2 or 3 at 48hr	30 (46)	122 (14)	<0.001
PGD 2 or 3 at 72h	28 (42)	93 (11)	<0.001
Rethoracotomy for bleeding	14 (21)	64 (8)	<0.001
Dialysis	18 (27)	63 (7)	<0.001
Atrial Fibrillation	9 (13)	91 (11)	0.52
Cerebrovascular event	1 (2)	12 (1)	0.63
Vascular complication	7 (10)	16 (2)	0.001
Posy-op pulsed steroid therapy	34 (52)	223 (26)	<0.001
Blood products (PRBCs)	23 (15-43)	6 (4-10)	<0.001
Secondary ECMO	3 (4)	17 (2)	0.18
Tracheostomy	23 (34)	90 (11)	<0.001
Ventilation time (days)	3 (1 – 17)	1 (1-1)	<0.001

In-hospital mortality	10 (15)	42 (5)	0.003

Secondary CE

Outcomes at Follow up

Freedom from biopsy-confirmed rejection, % (n)

	ECMO BTT (n=68)	Non-Bridged (n=849)	P-value
1 year	70 (7)	64 (2)	0.42
5 years	59 (8)	52 (2)	

Freedom from pulsed steroid therapy, % (n)

	ECMO BTT (n=68)	Non-Bridged (n=849)	P-value
1 year	60 (6)	52 (2)	0.17
5 years	40 (7)	35 (2)	

Freedom from chronic lung allograft dysfunction, % (n)

	ECMO BTT (n=68)	Non-Bridged (n=849)	P-value
1 year	95 (3)	96 (1)	0.46
5 years	61 (8)	66 (2)	

Freedom from retransplant, % (n)

	ECMO BTT (n=68)	Non-Bridged (n=849)	P-value
1 year	98 (2)	99 (1)	0.82
5 years	92 (4)	94 (1)	

				Secondary safety	**Duration of ECMO and deaths of patients on ECMO before transplantation** 19 patients required ECMO BTT but died before transplantation after a median support time of 9 (4-14) days. Death was due to bleeding (cerebral n=4, other n=2), acute haemodynamic decompensation (cardiopulmonary resuscitation n=2, right heart failure n=6), sepsis (n=4), massive haemolysis (n=1). Median support time of ECMO BTT in patients surviving to transplant was 9 (5-16 days)		
				Secondary CE	**Outcomes of patients on awake ECMO strategy Vs not awake** Outcomes did not differ between patients who underwent an awake ECMO strategy and those who did not (graft survival, P=0.38; patient survival, P=0.25; freedom from biopsy-confirmed rejection, P=0.53; freedom from pulsed steroid therapy, P=0.98; freedom from chronic lung allograft rejection, P=0.58; freedom from retransplant, P=0.46)		

8. Grade of evidence table

Use of ECMO versus no ECMO as Bridge to lung Transplant					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Survival at 1 year and 3 years	Ius et al 2018	9/10	Direct	Grade A	This outcome reports the likelihood of a patient being alive at 1 year and 3 years post-transplant post-transplant and is generally reported at the proportion (percentage) of patients alive at that time. All studies included in this review contained post-transplant survival as an outcome, all report this at 1-year post-transplant and two include survival at 3-years, and three report it at 5-years. Although there was some variation in the exact rates of survival at each of these time points, there was very high agreement that survival after transplant is no worse in critically ill patients requiring ECMO BTT compared with less ill patients who survive to transplant without ECMO bridging support The two best studies (Schechter et al 2016 and Ius et al 2018) both report survival at 1-year post-transplant. Schechter et al 2016 report cumulative survival at 1 year in ECMO BTT and non-bridged patients as 70.4% and 84.2% respectively, and additionally report 3-year survival as 64.5% and 67% respectively. Survival for ECMO BTT was not significantly different from those requiring no bridging support (P = 0.16). Ius et al 2018 report slightly higher rates of survival at 1-year: 79% in ECMO BTT patients compared with 90% in non-bridged patients. This difference was not statistically significant. They also report survival at 1-year conditioned to hospital discharge and this shows an even smaller difference between the groups with ECMO
	Hayanga et al 2018	7/10	Direct		
	Todd et al 2017	8/10	Direct		
	Kolaitis et al 2018	9/10	Direct		
	Schechter et al 2016	10/10	Direct		
	Lehmann et al 2015	6/10	Direct		
	Chiumello et al 2015	8/10	Direct		
	Toyoda et al 2013	7/10	Direct		

					BTT patients at 93% and non-bridged patients at 95%. This suggests that if patients bridged with ECMO remain alive in the early days post-transplant until discharge they have virtually the same rate of survival at 1 year. This was a recent, high quality study with a relatively large number of patients. Given the large body of evidence supporting this outcome, including several good-sized, high quality studies, there is a high degree of certainty that survival for ECMO BTT is no different from patients not requiring bridging.
Survival at 5 years	Ius et al 2018	9/10	Direct	Grade A	This outcome reports the likelihood of a patient being alive at 5 years post-transplant and is generally reported at the proportion (percentage) of patients alive at this time. One of the two best studies included data on survival at 5 years. Ius et al 2018 report the percentage of patients who are still alive at 5 years post-transplant as 65% of patients on ECMO BTT and 71% of patients non-bridged. This difference in survival was not statistically significant suggesting that there is no difference in 5-year survival of patients on ECMO BTT and those not requiring bridging support. This outcome has a relatively high degree of certainty as the outcome is very objective and it is reported by several studies with a good level of consistency. The evidence therefore suggests that two thirds of patients who receive ECMO BTT survive until at least 5 years and that this survival is no different to those not receiving bridging support.
	Hayanga et al 2018	7/10	Direct		
	Lehmann et al 2015	6/10	Direct		
Death on ECMO while awaiting transplant	Ius et al 2018	9/10	Direct	Grade A	This outcome refers to the deaths that occur in patients who are on ECMO while they are on the waiting list for a suitable donor for lung transplant. It is usually reported as a number or proportion of
	Schechter et al	10/10	Direct		
	Todd et al 2017	8/10	Direct		

	Lehmann et al 2015	6/10	Direct		the patients who are in the ECMO BTT group who die before transplant. The two best studies both include rates of death while on ECMO pre-transplant. Ius et al 2018 reported that 19/87 (22%) patients required ECMO BTT but died before transplantation after a median support time of 9 (4-14) days. Death was due to bleeding (cerebral n=4, other n=2), acute haemodynamic decompensation (cardiopulmonary resuscitation n=2, right heart failure n=6), sepsis (n=4), massive haemolysis (n=1). Schechter et al 2016 reported that of the 32 patients on ECMO at time of listing, 22 (68.8%) were transplanted, whereas 6 (18.8%) either died or their condition deteriorated such that they were removed from the list. However, these data are limited by reporting only deaths for those on ECMO at the time of listing so it is unclear how they relate to all patients who received ECMO BTT. There is a high degree of uncertainty as to the exact rate of mortality to expect in patients on ECMO BT while awaiting transplant as varying rates have been reported in the studies, but it is likely to be around 20-30%. This is likely to be due to small sample sizes in several studies and differences in the level of sickness and comorbidities of the patients put on ECMO, and advances in ECMO technology and safety which will affect survival. A lack of a control group for comparison also makes it difficult to interpret this data, however it should be noted that without ECMO 100% of the patients who need it would have died.
	Chiumello et al 2015	8/10	Direct		
Length of hospital stay	Ius et al 2018	9/10	Direct	Grade A	This outcome measure refers to the length of time that patients stay in hospital post-transplant. A shorter length of stay indicates a quicker recovery after the operation.
	Hayanga et al 2018	7/10	Direct		
	Todd et al 2017	8/10	Direct		

	Schechter et al 2016	10/10	Direct		The two best studies identified in this review both report length of hospital stay (LOS). Schechtrer et al 2016 report median length of stays of 15 days (IQR 10-24) for non-bridged patients, compared with 25 days (IQR 19-39.5) for those receiving ECMO BTT. The difference between the length of stay for these groups was not statistically significant. Ius et al 2018 report slightly longer median length of hospital stays for all transplanted patients; 23 days (IQR 21-28 days) for non-bridged patients and 42 days (IQR 26 – 67 days) for those on ECMO BTT. This difference was statistically significant (P<0.001). This outcome has a moderate level of uncertainty. It is objectively measured and has been reported in several studies with a similar pattern of outcome (longer LOS in ECMO BTT than in non-bridged patents). However, the exact LOS stay is not consistently reported and there is no consensus on whether differences in LOS are statistically significant between ECMO BTT and non-bridged patients.
	Chiumello et al 2015	8/10	Direct		
	Toyoda et al 2013	7/10	Direct		
Length of ITU stay	Ius et al 2018	9/10	Direct	Grade A	This outcome measure refers to the length of time that patients stay in ITU post-transplant. A shorter length of ITU stay indicates a quicker recovery after the operation. One of the two best studies identified by this review report data on ITU stay post-transplant. Ius et al 2018 found that the length of ITU stay in patients on ECMO BTT was a median of 11 days (IQR 4-23) compared with 2 days (IQR 1-4) in those without bridging support. This difference was statistically significant (p=<0.001) There is reasonable certainty that the length of post-transplant ITU stays are longer in patients who receive ECMO BTT than those who do not require bridging support. As only one recent study reports length of ITU stay the exact duration of ITU stay to be expected for an ECMO BTT patent remains unclear as it may vary centre to centre.
	Chiumello et al 2015	8/10	Direct		

Duration of pre-transplant ECMO	Ius et al 2018	9/10	Direct	Grade A	This outcome refers to the duration of time patients spend on ECMO before having a lung transplant. One of the two best studies included in this review reports the duration of pre-transplant ECMO. Ius et al 2018 report the median support time of ECMO BTT in patients surviving to transplant as 9 days (range 5-16 days). The majority (57/68) of these patients were awake on ECMO therefore had no MV. There is little certainty about the exact duration of pre-transplant ECMO in these patients, probably due to the different indications for ECMO at different centres and slightly different management of transplant waiting lists. However, it certainly seems to be the case that durations do not tend to exceed around 16 days in the majority of patients. This is likely to be due to the fact that once on ECMO, a patient becomes a high priority for available donor lungs.
	Hayanga et al 2018	7/10	Direct		
	Todd et al 2017	8/10	Direct		
	Chiumello et al 2015	8/10	Direct		
	Toyoda et al 2013	7/10	Direct		
Health-related Quality of Life (HRQL)	Kolaitis et al 2018	9/10	Direct	Grade B	This outcome refers to an individual's perceived physical and mental health over time. Patients who undergo lung transplantation and ECMO are critically ill and both procedures are high-risk and associated with complications and potentially long hospital stays and can therefore impact on an individual's perceived physical and mental health. Neither of the two best studies in this review reported this outcome, but it was included in one other study. Kolaitis et al 2018 reported changes in scores on 5 different measures of HRQL from pre-transplant to 6 months post-transplant in patients on ECMO BTT and non-bridged patients. Before transplantation, HRQL and depressive symptoms were similar among the groups, although non-bridged patients reported better baseline HRQL on two of the surveys (SF12-MCS and EQ5D). After transplantation, HRQL and depressive symptoms generally improved across both groups. Overall, peak improvement in HRQL and depressive symptoms was seen in the

					early period, within 6 months post-transplantation, and remained stable through to 12 months post-transplantation. The magnitude of these early improvements at 6 months varied by instrument: Estimates for change in the 5 HRQL measures over time from before transplant through to 6 months post-transplant include 17 (11-22) versus 21 (19 – 23) for ECMO BTT versus the non-bridged group on the SF12 physical component score; 11(9 – 13) versus 10 (9 – 11) on the Airways Questionnaire revised; 0.31 (0.20 – 0.42) versus 0.17 (0.13 – 0.21) on the EQ5D; and 4.8 (3.2 – 6.5) versus 3.5 (3.0 to 4.1) on the Geriatric Depression Scale The greatest improvement was seen in respiratory-specific HRQL, but there were also substantial improvements in health utility and depressive symptoms, and some improvement in generic mental HRQL. In summary, patients ill enough to require ECMO BTT achieve similar improvements in HRQL and depressive symptoms as those who do not require ECMO. These improvements are greatest in the 6 months post-transplant and then remain stable to 12 months. There is a low to moderate uncertainly with these conclusions, the study was high quality and used several different measures of HRQL which make the results reliable and valid, but only one study with relatively small sample size included measures of HRQL as an outcome. It is also not clear what duration of ECMO or level of sedation was experienced by patients which may affect generalisability. This is based on only one study with relatively small sample size that included measures of HRQL as an outcome.
Graft Survival	Ius et al 2018	9/10	Direct	Grade A	This outcome measure refers to the duration of time after the operation that the lung transplant remains functional, or the time from transplantation to the time when the lung transplant has irreversible failure and is no longer functioning. At this point,
	Hayanga et al 2018	7/10	Direct		
	Todd et al 2017	8/10	Direct		

	Schechter et al 2016	10/10	Direct		respiratory support is needed and a re-transplant may be required. This outcome is reported in the studies in the short term as rates of acute rejection (proportion of transplants that have been rejected), or in the longer-term as graft survival (the proportion of patients who have a surviving graft at various time points) or graft dysfunction (the proportion of patients with transplants that are no longer functioning at various time points). One of the two best studies in this review reports measures of both acute rejection and longer-term graft survival. Ius et al 2018 found higher rates of acute rejection (PGD score Grade 2-3) of the graft in ECMO BTT patients than in non-bridged patients at 24 hr (37% vs 15% respectively), 48 hrs (46% vs 14%) and 72hrs (42% vs 11%), all differences significant at p=<0.001. They also followed up graft survival at 1 and 5 years. They found that 90% of non-bridged and 79% of ECMO BTT patients had grafts that survived at 1 year, and 68% of non-bridged and 61% of ECMO BTT patients with grafts surviving at 5 years. These differences were not statistically significant (p=0.13) suggesting that graft survival is no worse in ECMO BTT patients. This relatively large and high-quality study suggests that acute rejection of the graft in the days immediately after transplantation is far more likely in ECMO BTT, but that in the long-term graft survival does not differ from non-bridged patients. The second of the two best studies in this review, Schechter et al 2016, reported the proportion of patients experiencing an episode of acute rejection before discharge only. This occurred in 8.7% of non-bridged patients and 10.8% in those receiving ECMO BTT, however these differences were not statistically significant. Other studies have not found any difference in rates of acute rejection immediately post-transplant but include major limitations (and none included a long-term follow up of graft survival).
	Ius et al 2018	9/10	Direct		

					Although all studies report a trend towards higher rates of acute rejection in ECMO BTT patients in the short-term immediately post-transplant, there is some disagreement over whether this difference is statistically significant. There are no clear methodological or clinical reasons why this might be the case. Long-term follow up of graft survival is only reported by one study but clearly shows that there is no difference between ECMO BTT and non-bridged patients at 1- and 5-years.
Post-operative complications	Ius et al 2018 Hayanga et al 2018 Todd et al 2017 Schechter et al 2016 Chiumello et al 2015	9/10 7/10 8/10 10/10 8/10	Direct Direct Direct Direct Direct	Grade A	Post-operative complications refer to any adverse consequences of having the lung transplant operation. This gives an indication of the impacts of ECMO on the safety of the subsequent lung transplant. The two best studies in this review both report post-operative complications. The most comprehensive list of the post-operative complications seen in ECMO BTT patients compared with non-bridged patients is provided by Ius et al 2018. The majority (57/68) of the patients in the ECMO BTT group were on an awake ECMO strategy and so did not receive concurrent MV. Several post-operative complications were more likely in ECMO BTT patients including bleeding (indicated by need for blood products and rethoracotomy for bleeding), renal failure (indicated by need for dialysis), vascular complications, need pulsed steroid therapy, tracheostomy, longer ventilation times, and higher in hospital mortality. Schechter et al 2016 included only two measures of post-operative complications; episode of acute rejection before discharge and new onset of dialysis. The incidence of new-onset dialysis in ECMO BTT patients was higher than in non-bridged patients (13.9% vs 10.3%) although this difference was due to chance. This is a high-quality study with a relatively large cohort of patients on ECMO, however it obtained data from a national organ sharing

					database so is likely to have been limited in the complications it reports due to only being able to include information recorded on the database. Three other studies report post-operative complications. Overall, there is evidence that ECMO BTT is associated with some increased post-operative complications. There is relatively high certainly that the risk of bleeding is higher in ECMO BTT patients as this has been found in all the studies that report this outcome. Higher risk of renal failure is a little less consistently reported with one of the three studies including this outcome finding it to be more common in ECMO BTT and two studies finding this not to be the case. There is therefore quite a high degree of uncertainty about this outcome. It is, however, difficult to give precise estimates of risk for each of these complications in ECMO BTT as the studies all use slightly different, indirect measures of the complications (e.g.blood transfusion vs re-thoracotomy for bleeding). Although there is some degree uncertainty due to small sample size in the single study that reports it (Todd et al 2017), there is clear suggestion that ECMO BTT is associated with far higher risk of delirium and myopathy with around 50% and 80% of patients experiencing each of these respectively. There is slightly more certainty that thrombotic and vascular events may be an increased risk int his procedure as this was also found by a larger, more robust study (Ius et al), albeit at a far lower rate (10% compared with 50% of ECMO BTT patients in Todd et al 2017.
Functional status	Todd et al 2017 Hayanga et al 2018	8/10 7/10	Direct Direct	Grade B	This outcome refers to an individual's ability to perform normal daily activities required to meet basic needs, fulfil usual roles, and maintain health and well-being.

					Neither of the two best studies in this review reported this outcome, but it was included in one other study. Todd et al 2017 included assessment of functional status with the Karnofsky scale index which is an assessment tool for functional impairment. A score of 50-70 on the Karnofsy Performance Status (KPS) Scale signifies inability to work but living at home and able to care for most personal needs. Score of 80-100 signifies ability to carry out normal activity and work with no assistance needed. Post-transplant Karnofsky scale functional status scores for each of the 12 patients undergoing ECMO BTT reported as between 70 and 100 (median=90, mean=87.5). The 1-year functional status in ECMO BTT group was not significantly different from the non-ECMO group (p=0.74) It was concluded that 1-year functional status was excellent in both groups. However, they highlight that this is in a select group of patients (under 65 years old, ambulatory before deterioration, no other organ dysfunction and good rehabilitation potential). These results suggest that there is no difference between the functional status of patients on ECMO BTT as those who do not receive bridging support, however there is a moderate degree of uncertainty around this. Although the study is of high quality and used a recognised and validated measure of functional status, the findings were based on relatively few patients in the ECMO group who have been selected for ECMO on the basis of being of good functional status before deterioration, therefore the extent to which these results would be generalisable to patients who were less well functioning or older is questionable.
Post-operative ventilation	Ius et al 2018	9/10	Indirect	Grade B	This outcome refers to whether or not patients required either MV or ECMO post-operatively, and in the case of MV the duration of time they needed it for before they could be taken off the ventilator to breath for themselves. A shorter time on MV, or not requiring
	Todd et al 2017	8/10	Direct		
	Toyoda et al 2013	7/10	Direct		

	Schechter et al 2016	10/10	Indirect		MV or ECMO at all indicates a faster recovery after the lung transplant. This outcome was reported by one of the two best studies included in this review. Ius et al 2018 looked at secondary ECMO requirements in patients who were on ECMO BTT and report no difference in the rate of secondary ECMO in patients compared with non-bridged patients (4% vs 2%, p=0.18). All patients on ECMO BTT in this study were on an 'awake' ECMO strategy which did not include concurrent MV. This study did not include data on requirement for MV post-operatively. Overall, there is some disagreement about whether ECMO BTT results in a greater likelihood of needing ECMO post-operatively. The different findings of the two recent large studies (Hayanga et al 2018 and Ius et al 2018) may be due to the different ECMO BTT procedure used, i.e. with or without concurrent MV.
Awake vs sedated ECMO	Ius et al 2018	9/10	Indirect	Grade B	This outcome refers to a variation in the ECMO BTT procedure. ECMO can either be delivered to patients who are sedated and bedbound, either for their comfort, success of ECMO application or because they are receiving concurrent MV, or it can be delivered to patients who are awake and able to walk and potentially take part in exercise. As described above, the studies included in this review differed in the ECMO BTT procedure received by patients both within and between studies. Schechter et al 2016 includes additional data for groups of patients who received MV + ECMO and MV alone (all sedated) which can be compared to outcomes for patients in the ECMO BTT group who received ECMO alone (awake). Survival at 3 years for patients on ECMO alone was not significantly different from those not requiring support (65% versus 67%, P = 0.16), however patients requiring either MV alone or ECMO + MV had significantly worse survival compared
	Chiumello et al 2015	8/10	Indirect		
	Schechter et al 2016	10/10	Indirect		

					with patients not requiring support 57% and 45% respectively (P < 0.0001 for both). These results suggest that awake ECMO is associated with better survival than sedated ECMO which requires MV and supports the survival outcome data (above) which demonstrates that survival for ECMO BTT is comparable to non-bridged patients. There is moderate to high level of certainty from the large, recent, high quality study by Schechter et al 2016 that awake ECMO confers a survival advantage over sedated ECMO that requires MV. However, the comparison of awake versus sedated ECMO is an indirect one as it is limited to a comparison of outcomes in subgroups of patients receiving the intervention as no cross-group comparison can be made as this is not a procedural variation in the non-bridged patients.

9. Literature Search Terms

Search strategy Indicate all terms to be used in the search	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients listed for lung transplant per NHS BT policy: NHSBT Policy 231/2 (http://odt.nhs.uk/pdf/lung_selection_policy.pdf)
I – Intervention Which intervention, treatment or approach should be used?	ECMO or interventional lung assist
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Supportive care

O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	Critical to decision-making: Survival to transplant Overall survival at 1 and 5 years Quality of life during the period of bridge to transplant and after transplant Important to decision-making: Adverse events including thrombosis, haemorrhage and infection Duration of ECMO (or ILA) Length of stay post transplant, both in intensive care and overall Cost effectiveness
Assumptions / limits applied to search	
Inclusion Criteria	Peer reviewed publications English language
Exclusion Criteria	Abstracts Letters Commentaries Conference papers Studies without comparators (including before and after studies) Papers published greater than 10 years ago

10. Search Strategy

	Search terms	Search details	Results
MEDLINE	1. (((extracorporeal membrane oxygenation) OR ECMO) OR interventional lung assist) OR iLA) 2. lung transplant 3. bridg* 4. (((#1) AND #2) AND #3)	Searched on Pubmed on 18th July 2018 Filters: published in last 10 years, English	402 articles

11. Evidence selection

Total number of publications reviewed: 402 titles and abstracts screened, 31 full text reviewed

Total number of publications considered relevant: 21

Total number of publications selected for inclusion in this briefing: 8

12. References

Bain JC, Turner DA, Rehder KJ, Eisenstein EL, Davis RD, Cheifetz IM, Zaas DW. (2016) Economic Outcomes of Extracorporeal Membrane Oxygenation With and Without Ambulation as a Bridge to Lung Transplantation. Respir Care, 61(1):1-7.

Chiumello D, Coppola S, Froio S, Colombo A, Del Sorbo L. (2015) Extracorporeal life support as bridge to lung transplantation: a systematic review. Crit Care, 22;19:19.

Cypel M, Keshavjee S. (2012) Extracorporeal membrane oxygenation as a bridge to lung transplantation. ASAIO J, 58(5):441-2

de Perrot M, Granton JT, McRae K, Cypel M, Pierre A, Waddell TK, Yasufuku K, Hutcheon M, Chaparro C, Singer L, Keshavjee S. (2011) Impact of extracorporeal life support on outcome in patients with idiopathic pulmonary arterial hypertension awaiting lung transplantation. J Heart Lung Transplant, 30(9):997-1002.

Fuehner T, Kuehn C, Hadem J, Wiesner O, Gottlieb J, Tudorache I et al. (2012) Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. Am J Respir Crit Care Med, 185(7):763-8.

Hayanga AJ, Aboagye J, Esper S, Shigemura N, Bermudez CA,D'Cunha J, Bhama JK. (2015) Extracorporeal membrane oxygenation as a bridge to lung transplantation in the United States: An evolving strategy in the management of rapidly advancing pulmonary dis - ease. J Thorac Cardiovasc Surg, 149: 291–296.

Hayanga AJ, Du AL, Joubert K, Tuft M, Baird R, Pilewski J, Morrell M, D'Cunha J, Shigemura N. (2018) Mechanical Ventilation and Extracorporeal Membrane Oxygenation as a Bridging Strategy to Lung Transplantation: Significant Gains in Survival. Am J Transplant, 18(1):125-135.

Hayes D Jr, Higgins RS, Kilic A, Kirkby S, Pope-Harman AL, Preston TJ et al. (2014) Extracorporeal membrane oxygenation and retransplantation in lung transplantation: an analysis of the UNOS registry. Lung, 192(4):571-6

Hoetzenecker K, Donahoe L, Yeung JC, Azad S, Fan E, Ferguson ND, Del Sorbo L, de Perrot M, Pierre A, Yasufuku K, Singer L, Waddell TK, Keshavjee S, Cypel M. (2018) Extracorporeal life support as a bridge to lung transplantation-experience of a high-volume transplant center. J Thorac Cardiovasc Surg, 155(3):1316-1328.

Ius F, Natanov R, Salman J, Kuehn C, Sommer W, Avsar M, Siemeni T, Bobylev D, Poyanmehr R, Boethig D, Optenhoefel J, Schwerk N, Haverich A, Warnecke G, Tudorache I. (2018) Extracorporeal membrane oxygenation as a bridge to lung transplantation may not impact overall mortality risk after transplantation: results from a 7-year single-centre experience. Eur J Cardiothorac Surg, 54: 334-340.

Kolaitis NA, Soong A, Shrestha P, Zhuo H, Neuhaus J, Katz PP, Greenland JR, Golden J, Leard LE, Shah RJ, Hays SR, Kukreja J, Kleinhenz ME, Blanc PD, Singer JP. (2018) Improvement in patient-reported outcomes after lung transplantation is not impacted by the use of extracorporeal membrane oxygenation as a bridge to transplantation. J Thorac Cardiovasc Surg, 156(1):440-448

Lehmann S, Uhlemann M, Leontyev S, Meyer A, Garbade J, Seeburger J, Laflamme M, Bittner HB, Mohr FW. (2015) Fate of patients with extracorporeal lung assist as a bridge to lung transplantation versus patients without--a single-center experience. Perfusion, 30(2):154-60.

Makdisi G, Wang I. (2015) Extra Corporeal Membrane Oxygenation (ECMO) review of a lifesaving technology. J Thorac Dis, 7(7): E166–E176.

Mohite PN, Sabashnikov A, Reed A, Saez DG, Patil NP, Popov AF, DeRobertis F, Bahrami T, Amrani M, Carby M, Kaul S, Simon AR. (2015) Extracorporeal Life Support in "Awake" Patients as a Bridge to Lung Transplant. Thorac Cardiovasc Surg, 63(8):699-705.

Nosotti M, Rosso L, Tosi D, Palleschi A, Mendogni P, Nataloni IF et al. (2013) Extracorporeal membrane oxygenation with spontaneous breathing as a bridge to lung transplantation. Interact Cardiovasc Thorac Surg, 16:55-9

Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM et al. (2009) CESAR trial collaboration. Efficacy and economic assessment of conventional ventilator support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicenter randomised controlled trial. Lancet, 17:374(9698):1351-63.

Schechter MA, Ganapathi AM, Englum BR, Speicher PJ, Daneshmand MA, Davis RD, Hartwig MG. (2016) Spontaneously Breathing Extracorporeal Membrane Oxygenation Support Provides the Optimal Bridge to Lung Transplantation. Transplantation, 100(12):2699-2704.

Todd EM, Biswas Roy S, Hashimi AS, Serrone R, Panchanathan R, Kang P, Varsch KE, Steinbock BE, Huang J, Omar A, Patel V, Walia R, Smith MA, Bremner RM. (2017) Extracorporeal membrane oxygenation as a bridge to lung transplantation: A single-center experience in the present era. J Thorac Cardiovasc Surg, 154(5):1798-1809.

Toyoda Y, Bhama JK, Shigemura N, Zaldonis D, Pilewski J, Crespo M, Bermudez C. (2013) Efficacy of extracorporeal membrane oxygenation as a bridge to lung transplantation. J Thorac Cardiovasc Surg, 145(4):1065-1071.